

Who shall go to university?

By clapping student quotas on British universities, the British Government hopes to save money. It could save as much, and make a more liberal system, if it encouraged a market in higher education.

ALMOST exactly twenty-one years ago, the then British Government took its courage in its hands and declared that all "qualified" young people would in principle have access to a place in higher education. By accepting literally overnight what was called the Robbins principle (after the chairman of the committee which recommended the change), the Conservative Government of 1963 agreed that the national interest of an industrialized state requires that higher education should be a right of all young people who could profit from the experience and not, as had previously been assumed, something of a privilege. This (for Britain) radical public policy was counted, at the time, a landmark in the development of the British educational system comparable in importance with the Education Act of 1944, which legislated for universal secondary education (and which was not fully implemented for more than a decade).

At the beginning of the prosperous 1960s, the British Government also fell naturally into the assumption that the extra cost of providing this public service would be met largely from public funds, which has been the practice ever since. But now a later British government, frightened by the cost of its predecessor's commitment, is seeking to abandon the Robbins principle — and is earning a thorough drubbing for its pains. Individual universities, universities collectively (represented by the Committee of Vice-Chancellors and Principals), the Royal Society and now a working party of the Royal Statistical Society have set out to tell the government why it is mistaken. The government has only itself to blame, for it is trying to solve the wrong problem in the wrong way.

The real problem, about which the government is right to be concerned, is the cost. Over the decades, British universities have become steadily more dependent on public funds for their costs (which are largely the costs of salaries). Since Robbins, the government has also paid students for being students, although never with such generosity that perpetual studentship was attractive and always with the application of a demeaning (for students) assessment of parents' capacity to meet maintenance costs. But for at least the past seven years, British governments have been alarmed that they might have signed a blank cheque — and have been looking forward for relief to the decline of the student age group expected in the coming decade. Even the Labour Government that went out of office in 1979 raised with the universities the issue of what they would do when there were more places in higher education than likely students. So far, the most tangible signs of the present government's hopes and expectations are the several demographic projections it has published in the past eighteen months. The most immediate expression of its interest is the preamble to the questionnaire put out by the University Grants Committee last year, threatening demographic contraction — and further financial contraction on top of that.

Detached view

The Royal Statistical Society's paper is written with a detachment that is all the more devastating for being almost a parody of what would be expected from dry statisticians. Taking a lordly view of the several alternative projections of the future demand for higher education that have been flying around in the past few months, the statisticians declare that most of the players in this arcane

numbers game have erred. Too often, they say, prognosticators break elementary rules by forming an indicator such as the age-participation rate in higher education, supposedly a measure of what proportion of each age group finds its way to a university or some comparable institution, by dividing the number of new entrants (of all ages) in some year by the number of young people in an almost arbitrarily chosen age group, say that of 16-year-olds. But the Royal Society, in its response to the universities' questionnaire, is highly commended for having seen that previous attempts to calculate the proportions of young people from different social classes entering higher education were flawed by their neglect of the upward social mobility which there has been even in Britain. And the British Government gets only poor marks, largely for having aggregated quantities (numbers of men and women, for example) that should not be lumped together and for not stating its underlying assumptions.

The upshot of all this is finally to undermine the British Government's opinion that it should be possible to restrict student numbers in higher education in the years ahead, and thus to save money, and yet not seriously to depart from the principle that all qualified young people can enjoy the opportunity of higher education. The government has been saying that by the early 1990s, the demand for higher education in Britain will decline by 13 per cent or more. The general consensus now is that if the rules remain unchanged, student numbers will decline by only half as much, and may even increase substantially if women seize an equal chance with men, or if upward social mobility continues even through the recession. The British Government now has no choice but to acknowledge that its sums are wrong. The delicate task of pointing this out in plain language falls to the University Grants Committee.

Shrinkage

That the British Government's hopeful predictions should be so thoroughly falsified is no surprise. It would be hard to find a single set of normal circumstances in any comparable country where, without artificial pressure from outside, a viable system of higher education has shrunk spontaneously. In Britain, there remain several crying needs still to be satisfied. There persists compelling evidence that the socially least favoured sections of the population go to higher education establishments less eagerly than they could, and should. The consistently smaller proportions of women than of men who seek higher education are further pointers to a need unsatisfied. And there is ample, if anecdotal, reason why the three-year courses which are still the standard diet of British universities are not long enough to be educative. The case for the contraction of British higher education is paper-thin. The effort should be abandoned.

But how otherwise can we save money? That is what the government will say. There are many obvious steps to take, which is why it is mystifying that a government which used to boast of its determination should, in this field, be so pusillanimous. Many universities and other institutions of higher education, the polytechnics for example, have found themselves operating more economically in the financial pressures of the past few years, and there is no reason why that process should not continue. By the standards followed elsewhere, in the United States for example, the ratio of full-time teachers to students is still generous. The



notion that students should be paid for their own maintenance (even at niggardly rates) while acquiring a decent education is a desirable luxury, the most seemly means by which participation can be made more equitable, but it is a luxury that should be sacrificed before the volume of higher education is itself constrained. What the British Government should now do is what it should have done when it was elected five years ago — create a market mechanism in higher education that will allow both institutions and students to find their proper levels, and then to spend what is necessary to meet obviously desirable social and national objectives of equity of access. □

Thanks but no thanks

The Royal Society has broken new and dangerous ground in its acknowledgements.

AUTHORS' acknowledgements are in danger of running wild. The brief paragraph at the end of the standard scientific article in which authors thank those who have helped them with their work, once the most stilted part of any scientific publication, is fast become the most informal — and confusing. Gone are the days when those thanked were also dignified with accepted forms of address — “Dr”, “Mr” or even, sometimes, “Sir”. More often than not, authors will substitute for the initials by which friendly colleagues are known bibliographically the sobriquets by which they are known about the laboratory (as in “I thank Bill Bloggs for a critical reading of the manuscript”). And while authors seem more meticulous than ever at recording the file numbers of the grants which they have enjoyed during the conduct of their work, they appear more than ever eager to distinguish between the kinds of services their colleagues have provided. Surprisingly, one of the pacesetters in this trend towards the informal is one of the oldest of all journals, the *Proceedings of the Royal Society*.

In a recent issue (Series A, 392, No. 1802, 8 March), colleagues are thanked in the usual way for “discussions” ranging from the “helpful” to the “enlightening” as well as for “technical assistance” (including, on one occasion, “in particular the maintenance of the computer”). Another colleague is credited with “an observation” that “allowed the work in paragraph 2 to be brought to a close much earlier than I had anticipated” while another described as a “student and guest of our laboratory developed a numerical program that solves the system of equations and boundary conditions”. Grant-making agencies are thanked in the usual way. One contributor to this issue writes “we also thank NATO for a travel and maintenance grant which made this work possible”. This is in sharp contrast with the acknowledgement at the end of the preceding article, which takes the form “This work was not supported by any military agency”.

The objective of this brief message is no doubt clear enough, but it must be wondered whether the Royal Society is fully aware of where the use of such acknowledgements may lead. (Strictly, the form is that of the negative acknowledgement.) Will contributors to *Proc. Roy. Soc.* in future be permitted to say that their work has been carried out “despite the failure of the Medical Research Council to provide the grant requested” or (for US contributors) “in the face of the difficulties caused by the enforcement of the Department of Defense memorandum DODD 2042.2”? On a more personal level, the management of the new acknowledgements may be even more difficult. Great dissension could be caused by the judicious use of phrases such as “with no help whatsoever from . . .”, “the scepticism of the head of my department notwithstanding” and “this work would have been completed two years earlier if it had not been for errors in the computer program written by . . .”.

Although some may argue that the introduction of this new style will make for greater openness in the exchange of scientific information, the risks are so great that only the most august periodicals can face them head-on. It is hoped that *Nature* will not be thought cowardly if, for the time being, it does not follow *Proc. Roy. Soc.*'s brave lead. □

Muddle about taxes

The international pattern of taxation is a brake on personal mobility and a problem for Unesco.

PEOPLE about to take sabbatical leave abroad ask two kinds of questions of themselves and their colleagues: “What will I do, with whom?” and “How can I arrange things so that I pay the least tax?” Questions of the first kind are professionally entirely proper; people rightly worry endlessly about them. Questions of the second kind usually take second place, with the result that the value of a sabbatical spell in a hospitable laboratory may be undermined by the domestic anxiety caused when local provisions for taxation are punitive — and are almost never fully understood. A little-noticed provision of the latest British budget (made public at the end of March, and which is not so much a forecast of government expenditure but of how the government proposes to meet that by taxation) is a splendid illustration of the pitfalls that abound.

The United Kingdom has arrangements with many (but not all) of its trading partners which avoid the worst of all horrors — double taxation — in the country of one's domicile and that in which one happens to be working. Partly out of recognition that short-term visitors to the United Kingdom would usually be paying taxes where they came from, would have found the move from one place to another a considerable expense out of a short-term salary and would not, in any case, enjoy the full range of social benefits that taxation is intended to finance, it has hitherto been the practice that visitors would not be taxed as severely as if they were permanent residents. No doubt many long-stay visitors, people posted to the United Kingdom for long periods by their employers, have gained financially, but the numbers have been small. But now that arrangement has been changed, and after a transitional period of five years, people earning incomes in the United Kingdom will be taxed as if they were permanent residents.

Superficially, this is merely another way of accomplishing an equitable objective which happens to be very similar to the way things are arranged elsewhere, the United States for example. The obvious snag, however, is that the change will be a further complication of a pattern of taxation internationally that is already almost too complicated for ordinary people. The certain consequence is that the new development will be a further impediment to mobility internationally — some at least of those who may have been planning to spend a sabbatical year abroad will be persuaded to stay at home, where the intellectual opportunities are not in any case negligible and where the system of taxation is at least already understood. Even more serious complications arise when people work for short spells for international organizations which may enjoy what is superficially described as tax-free status. On many occasions, it appears, income earned in this way is reckoned by the visitor's country of domicile to be taxable just as if it had been earned at home, and on other occasions there are adjustments to be made which are again impossible to understand, or at least to calculate in advance.

The complications of the kaleidoscope of taxes confronting professional people on the move is probably already a serious brake on the creativity of the scientific enterprise. After several years during which governments have regarded funds for fellowships for visitors in both directions as discretionary in the sense that they can be raided freely, it is distressing that still further obstacles should be put in the way of movement. With the migratory season in the Northern Hemisphere about to begin, there is an urgent need that the effects of international taxation on the mobility of professional people should be better understood. But the ideal is that there should be some generally recognized code of taxation for people such as scientists whose work requires that they should be free to move — and whose national governments eventually share the benefits. Is it too much to ask that Unesco, not conspicuously overburdened these days with worthwhile tasks, should help throw some light on this perplexing problem? □

Japanese telecommunications

Ministries clash over future of monopoly

Tokyo

THE United States has protested to the Japanese Government over compromises reached in two new bills intended to reform Japan's telecommunications industry. The bills, which have just been submitted to the Diet, are aimed at replacing the Nippon Telegraph and Telephone (NTT) monopoly of Japan's domestic telecommunications business by free competition in the supply of major services. A bitter dispute between the Ministry of International Trade and Industry (MITI), which took the United States' side, and the more conservative Ministry of Posts and Telecommunications (MPT) over the content of the bills held them up until the last possible moment for submission in this Diet session.

For the United States, what is at stake is entry into Japan's lucrative Value Added Network (VAN) market: the provision of telecommunications and computer equipment that permits the transfer of data from one computer to another. It is exactly these networks that Japan hopes will usher in the "electronic society" (see *Nature* 305, 364; 1983) in which a single set of terminal equipment will give access to a huge range of information-processing and transmission services, and businesses with different kinds of computers will be able to exchange information freely.

The United States is asking for the same complete freedom of access to VAN markets in Japan that is provided to Japanese companies in the United States. Despite some recent big orders, Japan buys only \$200 million worth of US telecommunications equipment each year compared with the \$1,300 million worth of Japanese equipment sold to the United States.

The new bills do go a long way towards allowing free foreign competition in that they provide for equal treatment of foreign and domestic companies. But companies wishing to offer large-scale VAN services will now have to register their plans with the government, while smaller companies will have to report only when they have commenced business.

These conditions are a huge advance over the original MPT demand that no company in which foreign ownership exceeds 50 per cent should be permitted to offer large-scale VAN services. What worries the United States, however, is that the bills do not say what is a "large" or "small" service, nor define what will have to be revealed to the government for registration. These conditions are to be decided later by government ordinance. The United States fears that the ministry could dictate the fees, business activities and facilities to be offered by foreign competitors and, on oc-

casional, handicap them.

MPT claims that it has opposed total liberalization of telecommunications because of their "importance to the economy" and because the VAN network handles "industrial and business secrets", even though the disputed section of the bill refers to the use of rented lines, not to their construction and ownership (which remains restricted to Japanese companies). MITI, on the other hand, cited concern to ease trade frictions for its support of the US side. But what also lies behind the worst inter-ministerial battle for years is MITI's desire to grab new territory: MITI claims VAN is an information processing service and thus within its jurisdiction while MPT argues that it is akin to telex.

Just a few weeks earlier, a similar battle with international repercussions broke out over software. Then, MITI argued that software is subject to patent law (controlled by MITI and giving only 15 years' protection) while the Ministry of Education argued that it was subject to copyright law (controlled by its cultural agency and giv-

ing 50 years' protection). Critics say that without changes in the practice of each ministry of hiring its own staff to work for it alone for life, ministries will continue to battle to extend their own influence, whatever the public interest.

As well as hanging on to control over business entry into VAN services, MPT has also fought for considerable retention of NTT's vast monopolistic powers — precisely what privatization was supposed to do away with. Plans to sell off two-thirds of NTT (whose assets are more than ¥10 million million (\$44,000 million), annual sales more than ¥4 million million (\$19,000 million) and with a third of a million people on the payroll) would have done much to help the government budget deficit but were thwarted by MPT opposition. Instead, the government is to maintain more than a 50 per cent share in the new corporation for at least the next five years and a part of the proceeds from the sale — which should take place in April 1985 — will go to NTT's research and development funds. Although giants such as IBM and AT&T can take the new corporation on, space for others will largely be determined by the exercise of what Isashi Shinto, president of NTT, calls self-restraint.

The whole legislation will be reviewed in three years' time and a US Embassy spokesman says his country will apply "continuous pressure". **Alun Anderson**

Chemical weapons

Proposals on ban treaty

Washington

WITH much fanfare, the Reagan Administration has presented a draft treaty that would ban the possession of chemical weapons. The treaty would complement existing conventions that prohibit the use of chemical weapons and either the use or possession of biological weapons.

The US draft spells out in exhaustive detail the mechanisms for verification, something the United States has insisted upon and which has been the stumbling block in the protracted negotiations with the Soviet Union. The draft, which was presented by Vice-President George Bush in Geneva to the 40-nation Conference on Disarmament, contains sweeping provisions for opening up the military and industrial facilities of all countries to international inspection. In addition to requiring systematic on-site inspections of declared stockpiles, production facilities and destruction facilities, the treaty would allow any party to demand — at 24 hours notice — an inspection of military or other facilities owned or controlled by a party nation. Furthermore, if an international "fact-finding team" to be set up by the treaty agreed, inspections would be ordered on 24 hours notice in any party country.

The Soviet Union has for many years resisted on-site inspection. Two years ago, however, Soviet Foreign Minister Andrei

Gromyko, in a speech to the United Nations, raised the possibility that the Soviet Union would accept limited provisions for on-site inspections. More recently, Soviet officials have indicated a willingness to accept on-site inspection of the destruction of existing declared stocks of chemical arms. The Soviets' immediate response to the American draft, however, has been to dismiss it as election-year propaganda. That view is shared by a significant number of President Reagan's political opponents in the United States, who note that the administration is also seeking funds from Congress to produce chemical weapons for the first time since 1969.

Under the draft treaty, each party would declare its stocks of chemical weapons, production facilities and plans for destroying its stocks, and would also provide regular production figures on chemical plants used to produce certain specified chemicals that could be used to manufacture chemical weapons. Parties to the treaty would have up to 10 years to finish the destruction of their stockpiles.

Countries would be allowed to retain up to one tonne of "super-lethal toxic chemicals" — with a lethal dose of less than 0.5 mg per kg via subcutaneous administration or 2,000 mg-min m⁻³ via inhalation — for research conducted for "protective" purposes. **Stephen Budiansky**

Cancer

Poor countries hit, too

THE World Health Organization (WHO) today launches a campaign in New York to convince Western scientists that the developing countries have cancer too — and that it can be controlled with simple measures.

According to WHO statistics*, of 4.3 million yearly deaths from cancer, 2.3 million are in developing countries. After the most dangerous first five years of life in developing countries, cancer is now one of the three major causes of death (the others being accident and circulatory disease), says WHO. And as life expectancy rises — it is now 68 in Sri Lanka, 64 in Kerala state in India and 62 in China — so does cancer as a cause of death. And the trend is rising rapidly as other infectious and parasitic diseases are brought under control, and as Western habits such as smoking increase.

WHO's cancer director, who has begun this campaign, is Dr Jan Stjernswärd, a Swede who until 1980 was director of the thoroughly First-World Ludwig Cancer Institute at Berne in Switzerland. But time spent in Africa, partly among the Masai tribe administering BCG immunotherapy ("when I was a witch doctor" he says) seems to have convinced him that there is more to be done about cancer in the developing world, where, he claims, one-third of cancers are preventable and one-third curable, often by primary health care and screening.

Stjernswärd is distressed that governments in many developing countries are adopting expensive radiotherapy and chemotherapy technologies on the Western model precisely when the development of these techniques in the West has been "plateauing off". At WHO, he has instituted a cost-effectiveness study of different therapies for oral cancer (caused mostly by tobacco-chewing) in India and Sri Lanka, which found that giving a "Rolls Royce" Western hospital-type treatment to one individual would actually cost 19 lives that could have been saved from cancer by early diagnosis, he says. Cancer is recognized and treated very late in developing countries, Stjernswärd finds. Yet a trial in India to see if village "barefoot doctors" could learn to recognize the early stages of oral cancer showed that barefoot diagnosis was as good as a specialist's after only two days' training.

According to data that Stjernswärd has collected, the most rapidly rising form of cancer in developing countries is lung cancer — probably caused by smoking. Nearly a quarter of young Chinese males now smoke, he says, as a symbol of affluence, and smoking is rising by 2.2 per

cent per year in China compared with a fall of 1.1 per cent a year in the West.

By continent, Asia has the most cancer deaths, in the world, 1,858,000 a year, followed by Europe with 1,398,000. North America has 447,000 cancer deaths a year. On current trends, world cancer deaths will rise to 8 million yearly by the year 2000.

The world's most common cancer is stomach cancer, followed by lung cancer; however, as stomach cancer is declining and lung cancer rising, the two will shortly change places, the WHO figures show. Liver cancer, closely associated with

hepatitis B, shows up at only half the rate of lung cancer but may be under-diagnosed. Stjernswärd has great hopes of hepatitis B vaccine, although its present cost — as derived from blood — of \$80 for three shots is far too expensive for health agencies in developing countries, where the average health budget is \$1–2 per head per year.

But China, remarkably, with its own production, hopes to bring the cost of blood-derived vaccine down to 50 cents for three shots. There will not be enough of that to go round, however, and the development of a cheap genetically-engineered vaccine — which seems just around the corner — would be very welcome.

Robert Walgate

Soviet agriculture

Salt in the wounds

SOVIET agriculture could face serious problems due to the salination of over-irrigated soils, Academician Anatolii P. Aleksandrov, president of the Soviet Academy of Sciences, warned recently at a high-level economic conference convened to review the progress of the "food programme" launched in May 1982. The purpose of this programme, Soviet publicists insist, is not merely to ensure sufficient food for the 260 million citizens of the Soviet Union — which they claim has already been achieved — but rather a radical change in Soviet eating habits, bringing the consumption of animal products up to "world levels" and cutting down on carbohydrates.

To feed the cattle and poultry needed for this new high-meat, high-dairy diet, the programme calls for a major switch from

device developed under the space programme to determine the composition of the soil of Venus has been modified by academy scientists to check the wetness of irrigated soils. Petr Pleshakov, the Minister of the Radio Industry, Aleksandrov reported, had "sworn" to put his device into full-scale production. Nevertheless, so far, "nothing had been done in this respect for many years." As a result local agronomy experts have no reliable information on the effects of irrigation in their area.

Aleksandrov's argument seems a little specious — the Venus-soil analyser was not invented for terrestrial purposes, and its adaptation seems rather to reflect party directives that the space programme should be seen to serve the national economy and that science should serve the food programme. It is difficult, too, to credit the implication that without the radars, it is impossible to monitor salinity.

According to Aleksandrov, such deficiencies as can be admitted in the food programme are the result of industry letting down the scientist. And sometimes the onus is with the planners — for instance, after the Institute of Biochemistry and Physiology had spent time and effort in developing a biotechnological method for producing a fodder protein from "paraffinaceous oil", a ministerial decision was made to conserve oil and work had to start on using natural gas instead.

Aleksandrov's special pleading on behalf of the academy scientists did not, however, touch on the shortage of younger scientific personnel for the food programme. According to a local conference in Estonia last winter, it is virtually impossible to attract young scientists into agricultural work. The monthly grant for a postgraduate student in agriculture is only 100 rubles (the average workers' wage is about 175 rubles per month) and those who begin postgraduate work immediately after their first degree get a reduced grant of only 85 rubles a month.

Vera Rich



cereals to fodder grains in the warmer (but drier) areas of the south and east. At present the Soviet Union has 18.6 million hectares under irrigation out of a total arable area of 214.6 million hectares, although part of this irrigated area is used for non-edible cash crops, notably cotton.

Aleksandrov did not state categorically that salination has yet occurred, but the tone of his remarks suggested that, at the least, the possibility is causing considerable concern. Already, it appears, a somewhat unlikely contingency scapegoat has been selected. According to Aleksandrov, a twin-frequency sidewise looking radar

*See "Estimates of the worldwide frequency of twelve major cancers" in the forthcoming (May) issue of *Bulletin of the WHO*, Vol 62, p.163 (1984) by D. M. Parkin, J. Stjernswärd, and C. S. Muir.

Soviet science

A declining influence?

Los Angeles

THE impact of Soviet science is surprisingly small and has markedly decreased in recent years, according to a study by Andrew Sessler, the plasma physicist who led the Lawrence Berkeley Laboratory for six years. Sessler first presented his findings at last year's international conference on Soviet Jewry in Jerusalem. "I wanted a topic where I could get some hard facts", he said.

The study has been based on the citation figures of the *Science Citation Index* published by the Institute of Scientific Information, Philadelphia. Sessler has compared data for 58 leading Soviet journals in 1975 and 1981. Since some Soviet accomplishments are not published in the open literature, the study concentrated on the impact, not the quality of Soviet science. Two measures were determined for each journal under scrutiny — a ranking by the number of original articles published in each periodical (by which test *Nauk Doklady* was ranked third in 1981) and the number of times a journal is cited elsewhere, or its "impact factor".

Between 1975 and 1981, Sessler found, the number of source items in Soviet journals fell by 18.9 per cent. During the same period, there was a worldwide increase of 67 per cent. Sessler says this could be explained if Soviet journals had adopted stricter editorial policies, but the citation rate of Soviet journals fell by 11 per cent between 1975 (86,737) and 1981 (77,130). This reduction, Sessler says, occurred despite a worldwide 12 per cent increase in the citation of all other scientific journals. In specific scientific fields, the *Science Citation Index* rating found that the best Soviet journals were on average 13 times less effective than the leading journals. Sessler concludes that "Soviet science is presently having very little impact on world science".

Why? One possibility is that Soviet science is hindered by its reliance on large block-funded institutes, Sessler said. Or the Soviet system of education may discourage young researchers' initiative. Certainly, he says, the Soviet system faces a crisis in instrumentation caused by revolutionary developments elsewhere.

Nevertheless, Sessler believes that Soviet science is certainly far stronger than is indicated by its measured impact. He guesses that there may be a shift in emphasis from basic to applied sciences, and that if more excellent scientists have been devoting their attention to military science, secrecy would have been increased. But political factors such as discrimination and reduced prestige for scientists could also be at work.

Sandra Blakeslee

UK forestry

Conservationists set to gain

THE British Forestry Commission is expected to make substantial concessions to conservation interests in a discussion document to be published early next month. The commission, which has been under increasing pressure over its *laissez faire* policies on broadleaved woodland, is likely to propose among other things that much stricter conditions should be imposed in future on private landowners seeking grant assistance for operations on ancient semi-natural woodland.

Conservationists attach great importance to the preservation of ancient woodland because it supports a greater diversity of wildlife species than modern stands, some of which are not native to the country. Since 1947, 30–50 per cent of Britain's ancient semi-natural woodland has been lost and the trend appears to be continuing. And the Forestry Commission has become the new bogeyman for conservationists because it has usually ignored the distinction between ancient and modern stands in its grant payments.

There is also disquiet because the commission is at present following government instructions to sell off many of its own woods, some of which have later been destroyed and replanted with fast-growing species. Companies have been established which exploit tax loopholes and take advantage of payments made by conservation bodies to protect ancient woodland. The Forestry Commission accordingly set in train a full policy review, which included consultations with the Nature Conservancy Council (NCC).

NCC has over the past few years been drawing up an inventory of ancient woods in Britain, which is now halfway to completion. The inventory compares present-day stocks with the mapped distribution of woodland earlier this century. The figures are not encouraging, according to NCC scientists. The Forestry Commission now seems ready to accept that the NCC list could be used as the basis for a classification that would be used to provide special protection to ancient woodland in future.

There are still problems, however. Mr John Kennedy, a member of the commission, points out that it is difficult to enforce legal protection for forests that can survive a change of ownership. And there is nervousness about making public the NCC list of woods that could be protected. Owners who want to guard the right to manage their woods as they wish could refuse access to surveyors if they suspected that any regulatory changes might not be to their advantage.

Despite the difficulties, the commission now seems to feel the time has come to clean up its reputation. Conservationists seem cautiously optimistic. One possibility would be to confer on ancient woodland

protection superior to that enjoyed by Sites of Special Scientific Interest, without creating more work for the already hard-pressed Nature Conservancy Council, which is responsible for the protection of such sites.

Tim Beardsley

Herschel's home imperilled

THE museum in the English city of Bath that commemorates the German-born astronomer William Herschel may have to close after the summer. The museum is in the house at 19 New King Street, Bath, where Herschel and his sister Caroline lived when he discovered the planet Uranus in 1781, and is Herschel's only surviving residence. Although Japanese astronomers have been frequent visitors during the four years the museum has been open, too few British visitors have materialized and no corporate sponsors have emerged.

Ironically, the Herschel Museum suffers from being in Bath which, although a tourist mecca, has too many museums. The city council has enough museums of its own to which it needs to attract patrons. The William Herschel Society has even had to pay to have a direction sign put up at the end of the street. The University of Bath, which has problems of its own with the Holburne of Menstrie Museum of Art, is unable to help, while another museum, the Postal Museum, is also under threat.

So, in spite of support from the National Maritime Museum, of which the Herschel Museum is an outstation, the Victoria and Albert Museum, which has lent a 1790 square piano as well as other furniture (Herschel was a musician), and the Bristol Museum, it seems that a unique museum is doomed.

Retired psychiatrists Elizabeth and Leslie Hilliard bought the house for the Herschel Society primarily because of their interest in its Georgian architecture. The garden has been replanted with herbs which Herschel's sister Caroline, an astronomer in her own right and compiler of the *Catalogue of the Stars*, would have used. John Mason, a member of the Herschel Society committee who restored the garden, dug up fused pieces of metal, the result of a recorded accident when Herschel was preparing lenses in his workshop which visitors now see. Enthusiasts of the Herschel Society (now copied in Japan) act as stewards and guides.

As things are, the Herschel Museum runs at a loss of more than £2,000 a year, which is being borne by the Hilliards. "My wife and I cannot carry on indefinitely — we're in our eighties", says Leslie Hilliard.

Laurence Dopson

Radioactive waste

Sea-dumping in doldrums

BRITISH radioactive waste disposal practices are to be examined by a remarkable independent review body established jointly by the government and the Trades Union Congress (TUC). A four-man committee has been appointed to look into existing evidence on the safety and environmental implications of sea disposal, and the government has undertaken not to attempt further sea dumps until the committee has reported.

Both the government and TUC have been embarrassed by last year's decision by transport unions to prevent Britain's annual dump at a designated site in the North Atlantic — the government because the industrial action effectively thwarted the first programme of the newly established Nuclear Industry Radioactive Waste Executive, and TUC because some of its constituent unions represent workers in the nuclear power industry. Recognizing common cause, government and unions have agreed that an independent review might resolve the issue.

At present, TUC says, it is opposed to the disposal of radioactive waste at sea, even for low-level material; it advocates land-based storage instead. Its chief complaint is that radioactive waste consultation procedures are "elitist" and keep the issue out of public view. But the unions' willingness to participate in a review of the question suggests that TUC may be open to persuasion.

Meanwhile, TUC has persuaded the government to accept on the new committee Mr Peter Taylor of the Political Ecology Research Group, an organization not noted for its sympathy to the nuclear industry. The government has countered by including on the committee Professor Brian Funnell of the University of East Anglia, a member of its own Radioactive Waste Management Advisory Group. The committee's chairman is Professor Fred Holliday, vice-chancellor of the University of Durham and a former chairman of the Nature Conservancy Council.

It might perhaps be questioned how much a four-man review can expect to achieve, especially since the Department of the Environment already has a large research programme investigating sea disposal options, including the emplacement of high-level wastes beneath the seabed, and the London Dumping Convention has a working group examining related questions. (The convention recently extended a moratorium on sea disposal until after next year's dumping season.) But Mr Taylor, for one, is undeterred, saying that existing models for dispersion of radionuclides at sea have been over-simplistic and that they fail to take into account the possible effects of lateral bottom currents and upwellings near land. He would also like to examine aesthetic attitudes to sea

dumping, whose importance is recognized by the International Commission on Radiological Protection but which have not so far featured in disposal assessments.

Tim Beardsley

Inaction on Med

MEDITERRANEAN beaches will remain polluted with heavy metals and untreated sewage at least for the time being, according to a decision taken by Mediterranean states last Friday, 13 April, in Athens, Greece.

It was a black day for the United Nations Environment Programme (UNEP), whose nine-year cooperative exercise on measuring pollution around the Mediterranean coast has been essentially ignored by the states that commissioned it.

The Egyptian UNEP executive director, Mustafa K. Tolba, pleaded with the meeting seriously to consider adopting environmental quality criteria for mercury in Mediterranean seafood and for the microbiological quality of bathing beaches, shellfish and the shellfish-growing areas. Said Tolba "If action is not taken now, the Mediterranean people may doubt how seriously committed you are to safeguarding the future of their sea".

To be cynical, however, it seems clear that so long as the tourists keep coming, while the cost of cleaning up sewage and industrial outfalls (or closing beaches and fisheries) is estimated to be many thousands of millions of dollars, and while the economic crisis persists, the Mediterranean states will be slow to comply with the finding that pollution levels are already too high for health in certain areas.

Robert Walgate

Visa blocked

Dr David Goldfarb, the Moscow Jewish biochemist, has had his visa for Israel cancelled on the eve of his departure and is now threatened with treason charges.

Although Dr Goldfarb had been told he could never leave the country since his work had brought him into contact with state secrets, the Academy of Science finally arranged his visa, apparently by appealing directly to the party central committee, bypassing the KGB. The academy scientists themselves felt threatened by the campaign of the military to have all sensitive areas of the life sciences classified as secret; they also wished to create an auspicious atmosphere before the meeting of the Federation of European Biochemical Societies (FEBS) in Moscow in June.

Last weekend, however, a KGB team went to Dr Goldfarb's apartment, confiscated his personal files and strain collection and told him he was under investigation for attempting to take to the West material of importance to national security. **Vera Rich**

US defence research

Pentagon climbs down on secrecy

Washington

THE quarrel between US universities and the Department of Defense (DoD) over proposed new restrictions on the publication of "sensitive" research may vanish as abruptly as it arose. At a meeting at the Pentagon last week, Dr Richard DeLauer, Under-Secretary of Defense for research and engineering, told a meeting of the DoD-University Forum that he did not favour a proposal developed by his own subordinate, Deputy Under-Secretary Dr Edith Martin, to create a new category of "sensitive" DoD-sponsored research that could not be published without DoD permission.

DeLauer's comments appeared to discomfit Dr Martin, who was present at the meeting, as much as it pleased the university representatives, led by Dr Donald Kennedy, president of Stanford University. Stanford is one of three universities concerned enough about the proposal to have written to DoD and to the White House science office warning that the proposal would prevent them from undertaking certain categories of research for DoD.

The contentious restrictions were part of an internal DoD report on the Pentagon's approach to international technology transfer. It said that DoD contracts for work that was both "applied" and "sensitive" should in future give the Pentagon the right to prevent publication of the resulting findings. Dr DeLauer, however, claimed to be mystified by the meaning of "sensitive" research. He said that the creation of such an ambiguous category would confuse DoD contract officers and was probably unnecessary; it would be better for DoD to rely on its existing powers of formal classification. That is what the universities said at a recent meeting of a forum subcommittee on export controls, only to be told by Dr Martin that it would be a mistake to adopt an "all or nothing" approach based on classification.

Meanwhile, both sides have good reason for patching up their differences as quickly as possible. DoD officials warned the universities last week that the 1985 bonanza proposed by President Reagan for DoD's basic research (about half of which ends up in the universities) was under fierce attack by the House of Representatives' armed services committee. Instead of growing by 6 per cent in real terms, as proposed in the president's budget, the budget could remain level or even decline by 2 per cent.

Dr DeLauer appealed to the universities to use their political influence to protect the budget proposals, saying that university presidents could do more to bend the ears of congressmen by inviting them to their campuses to "give them some gee-whizz and show-and-tell"

Peter David

Hungarian education

Flexibility hurts everyone

ON the heels of last year's reorganization of postgraduate education in Hungary (*Nature* 306, 216; 1983), the government is now turning its attention to the university system as a whole. Béla Köpeczi, Minister of Education and Culture, told the National Assembly (parliament) last week that Hungarian higher education must be made more flexible and provide "greater opportunities for the teaching of the natural and social sciences".

The content and structure of university teaching must be transformed, Köpeczi says, so as to emphasize student "self-education" and the development of "democratic forms and structures". Students should be given a freer choice of subjects while bureaucratic obstacles to university autonomy should be removed. In certain professions, "grades and levels" should be established so that students could obtain a first degree after one or two years' full time study, and, after a few years' practical work, return to full-time study.

Education in Hungary has been controversial at least since the late 1970s, when there were petitions and protests from parents fearing that the traditional *gymnasia* (grammar schools) were about to be abolished. Party officials have since condemned as the development of "intellectual dynasties", the tendency that the children of graduates themselves should have the wish and intellectual ability to go to university. (But the trend appears to have been exaggerated by the publicists; last week, Köpeczi reported that nearly 40 per cent of university students are now the children of manual workers.)

Meanwhile, the new proposal introduced last autumn (*Nature* *op. cit.*), aimed at letting graduates start working for a higher degree immediately after their first degree, seem simply to have served further to confuse an already complex system.

The new proposals, ostensibly aimed at stimulating the students' initiative and self-reliance, seem also to have increased their work-load. The number of optional subjects will be increased, while standards are to be raised in language courses.

Research facilities in universities will also be improved, and students will be allowed to attend courses in other faculties to broaden their outlook in professions other than their own. This concession may be intended to encourage students to change faculties during their undergraduate years and thus help to solve the perennial problem of Hungarian higher education — how to attract students into the sciences from the humanities, which now attract more students than the universities can accommodate or the job market can absorb.

Vera Rich

US state science

Californian scheme's success

Los Angeles

A PROGRAMME that gives professors extra money, students free training and industry new ideas is proving a spectacular success in California. Called Micro (the Microelectronics Innovation and Computer Research Opportunities Program), it was established in 1981 by legislative fiat to help the state's electronics and computer industry to maintain a competitive edge.

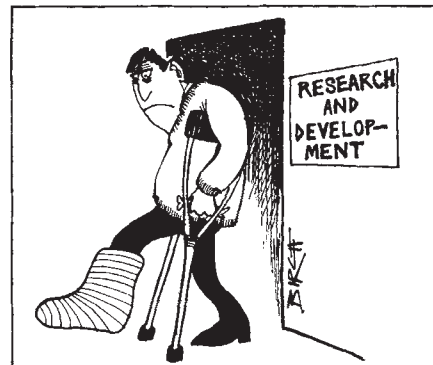
The idea, due to former Governor Jerry Brown, is one of the few to be given continued support by the new administration of Governor Dukemejian. Under the scheme, a professor works up a research plan and submits it to a company. The idea must be on the "cutting edge" of research and not related to near-term product development. If the company likes the idea, it supports at least half of the project's cost in cash and equipment whereupon the state, through the University of California budget, supplies the rest of the funds.

In Micro's first year, 31 projects on six campuses received more than \$2.1 million and 25 companies participated. Last year, 51 projects involved more than \$4.8 million and 33 companies. This academic year, 40 companies are supporting 58 projects costing \$3.9 million. The projects are in microelectronics, computer science and engineering.

The programme rests on two concepts: decentralization and entrepreneurialism. The science works "bottom up," says Al Barber, vice-chancellor at the University of California at Los Angeles. Everything depends on the individual professor, who initiates the proposal, garners support for

it, supervises and participates in the research and maintains liaison with the partner company, represented by a single person empowered, with the professor, to decide what is interesting and worth pursuing.

All benefit — students by working on advanced research projects, by access to ultramodern equipment and fellowship support, professors by an alternative source of funds, while the university gleans



research results, patent rights and trained students for half the usual cost. Industry gains new research ideas, a talent pool of young scientists in the community and strengthened university ties.

Most projects involve advanced computer development, but one unusual study is aimed at the microcomputer control of ski bindings. Since 95 per cent of all ski bindings are sold by European manufacturers and the worldwide market exceeds \$500 million, the California researchers hope that safer microcomputer controlled bindings could crack that near-monopoly.

Sandra Blakeslee

Wildlife photographers, not necessarily of the greater horseshoe bat (right), are invited to enter Britain's "largest ever" wildlife photographic exhibition. Sponsored by Prudential Assurance in association with BBC Wildlife Magazine, The Fauna and Flora Preservation Society and the Natural History Museum, the closing date for the competition is 29 June. Details of the prize categories can be obtained from the British Museum (Natural History), Cromwell Road, London SW7 5BD, UK. The competition is open to professionals and amateurs and includes categories for various age groups.



Non-Proliferation Treaty woes

SIR — Your leading article (*Nature* 8 March, p.97) makes some telling points on the finer nuances of international nuclear politics. I should like to comment on one of the issues you raise: that of the imminent danger of the collapse of the Non-Proliferation Treaty (NPT).

There seem to be two contentious issues that the current nuclear weapons states refuse to address seriously. First, Article VI of the NPT requires them to "pursue negotiations in good faith on effective measures relating to cessation of the nuclear arms race". There is scant evidence that any of the nuclear weapons powers is doing any such thing.

Second, at least two of the current nuclear weapons states — Britain and the United States — reserve the right under the "safeguards" agreements signed with the International Atomic Energy Agency (IAEA) in 1978 and 1979 respectively to withdraw special nuclear materials from the civilian stockpile for military purposes if so deemed necessary by "supreme national security" considerations.

Indeed, Dr Charles F. Gilbert, then acting Deputy Assistant Secretary for Nuclear Materials at the US Department of Energy, told a congressional committee in 1981 that the attempt to amend the US Nuclear Waste Bill by Senators Hart and Simpson, which would prohibit the "mining" of plutonium produced in civil nuclear reactors for military purposes, was not supported by the US administration. Gilbert said that the Hart-Simpson amendment would "restrict our ability to obtain plutonium and might have serious consequences if the United States should need additional (military) plutonium".

Events since have shown the US administration is indeed planning a nuclear weapons programme expansion that will demand a considerable build-up of its fissile material stockpile for warhead manufacture. In 1982, Dr Herman E. Roser, Assistant Secretary of Defense Programs, US Department of Energy, told a congressional hearing that, with regard to the possible diverting of civilian plutonium to the US defence programme, "I do not believe we should foreclose that option because I don't think we should foreclose any options, when it comes to the security of this country". Yet Deborah Shapley reported (*Nature* 297, 255; 1982) "Critics of DoE's plans argue that if the United States starts taking civilian spent fuel from its weapons programme, it will not have a leg to stand on when it tries to dissuade other countries likewise".

This criticism applies equally to the United Kingdom Government. Article 14 of its "safeguard" agreement with IAEA and Euratom states that the British Government may withdraw special nuclear materials from the scope of the agreement for "national security reasons". Although

the British Government states it has no intention of exercising this right, it continues to reserve the right legitimately to divert civil nuclear materials for military purposes, if circumstances of dire national security demand so.

Nature's proper worry that the NPT may collapse at the 1985 Review Conference is certainly justified. The 1980 Review Conference only narrowly avoided such a fate. Events since then have exacerbated the situation, with suggestions that Argentina and Pakistan (Note 10) both non-signatories to the NPT, now have facilities to make their own nuclear weapons.

The 1985 NPT Review Conference offers a real chance for a resurrection of trust and confidence between nations. It seems the nuclear weapons states must show willingness to take the first positive steps if the conference is to avoid disaster. The scientific community surely have a duty to help make sure this disaster does not occur.

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Plagiarism in texts

SIR — It is difficult to see how any text book can be written without some kind of plagiarism since there can rarely be a scientist who can fill a book with the results of his own researches. Authors of larger text books are usually academics busy with lectures, research and administration and generally delegate the work to secretaries who are asked to rewrite such and such a piece incorporating a few additional pieces of recent research. The stage is not set for convergent evolution, so why not accept the fact?

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Citations overlooked

SIR — In my review of John Nicholson's *Men and Women* (*Nature* 307, 764; 1984) I wrote that the author "rarely cites primary sources". This remark may have been misleading, since although he rarely cites them in the text, he does quote some primary sources (together with secondary ones) at the back of the book. Although each reference includes the page number to which it refers, it would take a very diligent reader to connect the references with the text, since the references for each chapter are arranged in alphabetical order, not in the order of the pages to which they relate.

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Invisible usage

SIR — The *Shorter Oxford English Dictionary* defines the word "viable" as, *inter alia*, "able to maintain a separate existence" and, *pace* Dr Gill (*Nature* 307, 312; 1984), it is in this sense that it is usually used in embryology and neonatology. A "viable" unborn child is, in fact, one that is capable of surviving if separated from its mother, when incidentally its life is protected under the Infant Life (Preservation) Act 1929.

A fetus which can in no circumstances survive apart from the mother, when for example its lungs are not yet capable of being inflated, ought not to be described as "viable", even though "in the appropriate environment", that is, in its mother's womb, "it is indeed capable of maintaining its life, given adequate oxygen and nutrition". It is, however, possible, and perhaps useful, to draw a distinction between a fetus which is "previable", meaning that although it is not yet viable it is capable of later becoming so, and one that is "inviable" which, although still alive, can in no circumstances be expected to achieve viability.

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SIR — Your correspondent (*Nature* 307, 312; 1984) must have reasons of his own to obfuscate the meaning of "previable". The editors of *Butterworths Medical Dictionary* (Butterworths, 1965) do not share his plight, and define the word to mean "before the point at which extra-uterine existence is possible". What can be plainer than that?

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Xiaoping first?

SIR — First name or last name first? "The Second Nuclear Wars Composite" (*Nature* 306, 509; 1983) did little to settle the issue. This case in particular, the Chinese word "xiao" means diminutive and "ping" signifies peace. In a country officially espousing peace, millions of small children are endeared by the nickname Xiaoping, which happens to be Deng's given name. To call him by that is perhaps seventy years too late.

Gerontocratic tradition and authoritative reverence demand all respectable Chinese except those in the inner circle of power to use his full name, Deng Xiaoping. Westerners may be forgiven for calling him Deng, his surname. But to list "Reagan, Brezhnev, Mitterand, Thatcher and Xiaoping" is almost like saying "Reagan, Mitterand, Thatcher, Deng and Lenya."

RICHARD J. WANG

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Causation of AIDS revealed

Secretary of Health Margaret Heckler announced in Washington this week that the retrovirus responsible for AIDS has been identified by Gallo's group at NIH; Montagnier's group in Paris has helped.

THE greatest obstacle in the study of the acquired immunodeficiency syndrome (AIDS) has been the inability to identify the responsible aetiological agent. The initial stage of the epidemic has been one of recognition and description¹⁻⁵. The publication of four papers this week in *Science* (dated 4 May) by Dr Robert Gallo (National Cancer Institute) and co-workers on a novel human T-cell lymphotropic retrovirus, HTLV-III, provides compelling evidence for a primary association of this virus with the disease. Preliminary seroepidemiologic data indicate that nearly all AIDS patients and patients with AIDS-related disorders such as unexplained generalized lymphadenopathy have antibody to HTLV-III antigens. The prevalence of seropositivity among asymptomatic persons at high risk for AIDS is currently being determined. HTLV-III was readily recovered from a significant number of patients with AIDS and the lymphadenopathy syndrome.

The hypothesis that AIDS is caused by an immunosuppressive retrovirus tropic for helper T-cells has been advanced by Essex and colleagues⁶⁻⁸. They showed an increased prevalence of seropositivity among AIDS patients and certain high risk groups, such as haemophiliacs, for antibody which recognized envelope antigens of HTLV-I and HTLV-II. Similarly, Chermann, Montagnier and co-workers at the Pasteur Institute in Paris have reported isolation of lymphadenopathy-associated retrovirus (LAV) from AIDS patients^{9,10}.

LAV is tropic for helper T-cells. Subsequent characterization will define its relationship to HTLV-III. Proving that HTLV III is the cause of AIDS cannot be readily done in accord with Koch's postulates. Nonetheless, such evidence can be obtained in cases of transfusion-associated AIDS, wherein a person lacking lifestyle risk factors for AIDS contracts the disease after receiving blood from a person who either has AIDS or is at risk for the disorder^{11,12}. Demonstration of seropositivity and/or recovery of HTLV III from such donor and recipient pairs will provide further data for causation. Similarly, prospective studies proving that seroconversion, particularly with recovery of HTLV-III, is both a necessary and sufficient event for development of AIDS will allow us to state definitively that this virus is responsible for the syndrome. Based on other viral diseases transmitted by sexual, blood and needle routes, such as hepatitis-B, we can expect a spectrum of clinical manifestations follow-

ing HTLV III infection. Host or environmental factors may well modulate susceptibility and severity of clinical disease. Indeed, HTLV I is isolated from seropositive persons in endemic areas of Japan and the Caribbean who do not develop adult T-cell leukaemia.

The geographic distribution of AIDS is an unusual one, particularly the occurrence of the disease in Haiti and Central Africa¹³. Identification of a region with high seropositivity among the general population should provide circumstantial evidence regarding the geographic origin of the virus. Although HTLV I and HTLV II have been recovered from homosexual men with AIDS in the United States it is unlikely that the seropositivity reported by Essex and co-workers among such high-risk persons using an indirect fluorescence assay was acutely measuring antibody cross-reactivity to HTLV III.

AIDS research can now shift from studying indirect manifestations of the AIDS agent to a direct examination of the interaction of HTLV III with T-lymphocyte subpopulations, B-cells, monocyte-macrophages and haematopoietic stem cells. All of these cell types have been noted to be dysfunctional in AIDS, and understanding how this virus disrupts so many immune responses should provide important insights into the murky web of interacting cell populations. We can also now ask whether infection with HTLV III is permanent or transient, and whether persistent infection is a requirement for development of clinical disease. Epidemiologically, data have been accumulated indicating a hierarchy of risk for AIDS upon exposure to body secretions and excretions with semen, stool and blood thought to be the most contagious substances. With direct identification of the causative virus, we can now verify how the disease is transmitted and whether surface fluids such as sweat, saliva and tears could be infectious.

It has often been said that AIDS offers a unique opportunity to understand basic mechanisms of the interaction of the cellular immune system with infectious agents and in the pathogenesis of certain neoplasms. Is there a direct role for HTLV III in the genesis of Kaposi's sarcoma or B-cell lymphomas, frequent tumours in these patients? These neoplasms are epidemiologically related to cytomegalovirus and Epstein-Barr virus respectively. Is there a direct interaction between DNA viruses and retroviruses such as HTLV III? Will

therapy directed against HTLV III, with improvement or restoration of immune status, result in the body's own defence mechanisms limiting such neoplasms?

At present, there is no effective therapy for AIDS. Determining the effects of various therapeutic agents, such as alpha and gamma interferons and interleukin-2, on HTLV III infected lymphocytes may provide direction for development of rational therapy for the syndrome. Furthermore, studying whether antibody is protective against HTLV-III infection will determine the utility of vaccination. Certain monkeys may be amenable to HTLV-III infection and serve as models for vaccination in man. But given the apparently long incubation period of AIDS¹², it will be difficult to determine whether seropositive individuals who do not have recoverable virus are indeed protected.

The psychological, economic and logistical impact of identification of the cause of AIDS is formidable¹⁴. It is estimated that there are now 10-20 million sexually active homosexual men, 15,000 haemophiliacs, 500,000 Haitians, and 4 million blood donors in the United States. Screening such populations is a staggering enterprise. Not yet fully knowing the ultimate clinical significance of seropositivity and/or recoverable virus in such populations will compound the complexities of testing. Difficult lifestyle questions concerning continued sexual activity will certainly arise for seropositive persons.

AIDS is a tragic disease with considerable morbidity and mortality. The work by Gallo and colleagues constitutes a turning point in the struggle with this epidemic. Identification of its cause should rapidly provide accurate information on the extent and pathogenesis of the disorder; prevention and therapy will require long-term efforts.

Jerome E. Groopman

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Oncogenic intelligence

Oncogenes and inositol lipids

from Bob Michell

THE discovery of oncogenes opened a new era in studies of the control of the proliferation of both normal and malignant cells. The suspicion that the proteins coded by cellular oncogenes are participants in normal biochemical pathways essential to cellular growth control, and that these may go subtly awry in malignancy, is strengthened by the knowledge that the proteins encoded by oncogenes include a secreted growth factor¹⁻³, a homologue of a growth factor receptor⁴ and several 'tyrosine-directed protein kinases'⁵ which catalyse the same reaction as some activated growth factor receptors (see ref. 6). What has been lacking is any clear knowledge of the nature of the cellular control pathway(s) affected by these proteins. But now studies by two communicating research groups indicate that some oncogene products act on the receptor-activated pathway in which the breakdown of an inositol lipid is stimulated, leading via an increase in cytoplasmic Ca^{2+} concentration and activation of protein kinase C to cell proliferation^{7,8}.

The primary evidence of both groups is that certain oncogene products can act as inositol lipid kinases. Thus, Sugimoto *et al.* show that purified pp60^{v-src}, the tyrosine kinase coded by the *src* oncogene of Rous sarcoma virus (RSV), can phosphorylate phosphatidylinositol (PtdIns), phosphatidylinositol 4-phosphate (PtdIns4P) and 1,2-diacylglycerol (1,2-DG)⁷. And Macara *et al.* demonstrate that p68^{v-ros}, the tyrosine kinase coded by the *ros* oncogene of the avian sarcoma virus UR2, can phosphorylate PtdIns⁸. The final product of the pathways of inositol lipid biosynthesis is phosphatidylinositol 4,5-bisphosphate (PtdIns4,5P₂), which is hydrolysed when appropriate receptors are activated⁹⁻¹¹.

Sugimoto *et al.* found that the transformation of fibroblasts by a temperature-sensitive mutant of RSV led to a large increase in the cellular content of PtdIns4,5P₂, PtdIns4P and phosphatidate only at the permissive temperature⁷. Cells transformed by UR2 showed both an increase in ³²P-labelling of PtdIns4P and PtdIns4,5P₂ relative to other phospholipids and an accumulation of inositol trisphosphate (InsP₃) and bisphosphate.

A clear and unbroken association between rapid inositol lipid turnover and rapid cell proliferation was first clearly established by Diring¹² and has been maintained in all subsequent studies (reviewed in refs 13 and 14), suggesting that the turnover of these lipids is either an essential element in control of cell proliferation or an invariable consequence of that proliferation. The former view is supported by the fact that several, though not all, receptor-directed agents that stimulate cell proliferation cause a very rapid increase in the turnover of inositol lipids, long before any overt proliferative response. The initiating reaction is probably the breakdown of PtdIns4,5P₂ to 1,2-DG and InsP₃ (refs 9-11), with these two cellular messenger molecules activating, respectively, protein kinase C (which is also the cellular target of tumour promoters¹⁵) and the mobilization of Ca^{2+} ions from an intracellular store¹⁶. The new data suggest that one way in which some oncogenes (and possibly also growth-promoting hormones that activate tyrosine kinases) act is by enhancing the kinase activities responsible for supplying PtdIns4,5P₂, either by acting as inositol lipid kinases or by modifying the activities of the intrinsic cellular kinases.

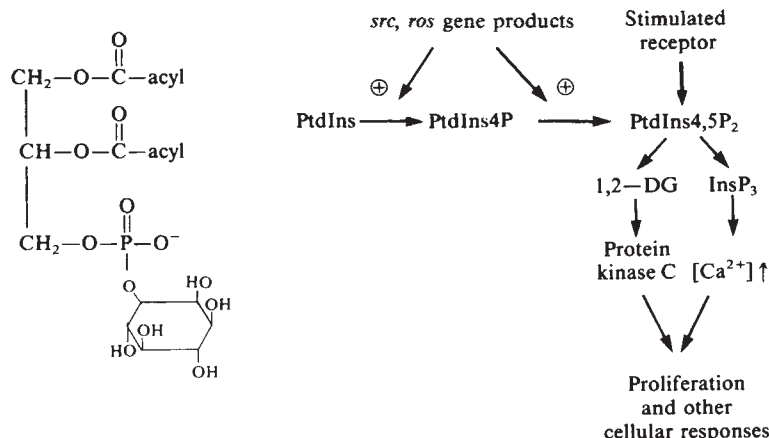
Why should the breakdown of PtdIns4,5P₂ be a normal control reaction

in nonproliferating cells and also a stimulus to proliferation? Possibly there is some sort of threshold of signal intensity that has to be exceeded before proliferation is triggered in competent cells. This might provide a rationale for the frequent observation that a combination of tyrosine-kinase-directed stimulus (insulin, epidermal growth factor) and PtdIns4,5P₂ breakdown directed stimulus (bombesin, vasopressin, prostaglandin F_{2a}) is a much more potent activator of proliferation than is either stimulus alone^{17,18}. In this interpretation it would be envisaged that one stimulus enhances the supply of substrate to the signalling reaction activated by the other stimulus, so leading to a greater intensity of signal input to the cell than can be achieved by either stimulus alone. An exception would be platelet-derived growth factor, which seems to be a potent stimulus both to a tyrosine kinase¹⁹ and to inositol lipid breakdown²⁰.

If activation of proliferation does indeed require a combination of a high rate of PtdIns4,5P₂ synthesis and a signal that activates PtdIns4,5P₂ breakdown, then any oncogene product that could enhance the activity of either of these pathways might act as a proliferative signal, provided that normal environmental signals ensure some activity of the other arm of the system. If so, it may be anticipated that oncogene products that control, have or may have kinase activity (*sis*, *erb-B*, *src*, *ros*, *fps*, *fes*, *abl*, *yes*) will serve to control PtdIns4,5P₂ supply, whereas other oncogenes might encode proteins (for example, receptors, PtdIns4,5P₂ phosphodiesterase or protein kinase C) involved in the pathways in which PtdIns4,5P₂ breakdown acts as a signal. There is some evidence that the latter pathways involve a guanine nucleotide-binding regulatory protein²¹: could this be p21, the GTP-binding protein coded by *ras* oncogenes? □

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Structure of phosphatidylinositol (left) and diagram of interactions between oncogene products, cell-surface receptors and inositol lipid metabolism (right).

Geophysics

Contraction and stretching in basin formation

from Norman H. Sleep

BASINS on the continental shelves of passive (or Atlantic) margins and platform basins within the continental interior are generally a few hundred kilometres wide and contain several kilometres of nearly flat-lying sediments. The processes underlying the deposition of these sediments have been the subject of extensive investigations in recent years, particularly in the context of oil exploration. Because rocks deposited near sea level are encountered at great depths in bore holes, deposition is thought not to be a simple process of filling in pre-existing depressions but to be controlled by subsidence of the underlying bedrock. Recently, Cochran¹ has presented a detailed model which attributes the subsidence both to thermal contraction and to stretching of the lithosphere.

Cochran's model is grounded on the basic concepts of the formation of passive margins by continental break-up²⁻⁵. Geologically, a continental rift valley widens into the young margin of a small ocean and finally into the mature passive margin of a major ocean. As a rift develops along the nascent margin during continental break-up, hot mantle is emplaced beneath it in the same fashion as mantle is emplaced at a mid-oceanic ridge. After the rifting event, thermal contraction of the lithosphere beneath the margin causes subsidence, which is followed by deposition of sediments. Crustal thinning during break-up, the second feature of Cochran's model, is necessary if the process is to produce a basin. Without crustal thinning, thermal expansion of the lithosphere would produce an uplift which would return to sea level when it subsided. Erosion during the thermal uplift as the mechanism of crustal thinning was overemphasized by the earlier workers, myself in particular⁵, because our data were obtained from boreholes landward of the region of significant stretching and because we were impressed with the major unconformity which followed break-up in these landward areas. We now know that in the more seaward areas, there is no major break-up unconformity; the amount of crustal thinning in the seaward areas is so great that it must be produced by stretching.

Although the original papers on thermal contraction of the lithosphere were published early in the plate tectonic revolution, the idea found little immediate acceptance and it was not until 1976 that the mechanism was discussed in a summary of a conference on Atlantic margins⁶. A partial explanation for the initial resistance is that American geophysicists believed that a

proto-ocean existed in the Atlantic and thus excluded the possibility of continental break-up⁷ or they believed that the break-up was Permian and thus too early for thermal contraction to cause Cretaceous subsidence (for example, ref. 8; the presently accepted age of the rifting of the East Coast of the United States is near the Triassic-Jurassic boundary⁹). Acceptance of plate tectonics by scientists studying basins was also slower than in other fields of earth science. For example, J. Lamar Worzel, a leading researcher on continental margins, remained strongly sceptical of plate tectonics until at least 1976 (ref. 10), by when proponents of thermal subsidence^{5,11-13} had convinced a significant portion of the geological community.

The oil shortage and a wealth of new data encouraged the more detailed physical studies which form the immediate basis of Cochran's model. In particular, Watts and Ryan¹⁴ introduced the concept of 'driving load' — the amount of subsidence which would have occurred in the absence of sediment loads and regional redistribution of loads by flexure of the lithosphere. They extracted the history of the driving load from the record of sedimentation on the Atlantic coast of the United States by correcting for sedimentary processes such as compaction, weight of the sediments and changes in water depth. McKenzie¹⁵ subsequently proposed a simple one-dimensional thermal model of continental break-up in which the lithosphere is uniformly and instantaneously thinned by stretching during rifting. In general, this process involves rapid subsidence as the crust is thinned during stretching, followed by gradual subsidence as the lithosphere cools. Subsequent work on basin mechanics, such as Cochran's, has involved combinations, modifications and applications of the methods of Watts and Ryan and of McKenzie, including determination of palaeotemperatures and petroleum maturity within the sedimentary column.

Clearly, McKenzie's model is a simple but elegant approximation. Atlantic margins and interior basins have finite width and even at plate tectonic rates it takes several million years to stretch the lithosphere. For example, the periods of Permian stretching in the Basin of Paris and Tertiary stretching in the northern Red Sea may last more than 20 Myr. Cochran has studied gradual stretching of a finite two-dimensional basin¹. For rifting events of greater than 20 Myr his results are significantly different from those of the one-

dimensional model because of the amount of cooling that occurs during the rifting stage. The post-rift subsidence is reduced by 25 per cent at the centre of the basin and the lateral flow of heat causes minor uplift on the flanks of the basin. After the rifting ends, the lithosphere becomes more rigid and the cooling of the material beneath the rift causes subsidence to extend over the flanks of the rift valley. The basin becomes progressively wider as the lithosphere thickens and stiffens with time. Considerable overestimates of the palaeo-heat flow of the basin result if the gradual syn-rift sedimentation is attributed to post-rift thermal contraction.

Cochran has developed a good starting model for application to an actual basin. How useful it will be will depend on how precisely uniform is the stretching in the crust and mantle lithosphere; stretching may involve nearly intact blocks and highly attenuated zones. Furthermore, the assumption that lithospheric heating is directly related to crustal thinning by the geometry of stretching, which gives McKenzie's and Cochran's formulations much of their elegance, is open to question. Substantial heating of the lower lithosphere, probably by bulk delamination and replacement with hot asthenosphere without significant stretching, is common around hot-spot volcanoes, such as Hawaii¹⁶. Lithospheric heating is thus possibly more widespread than crustal thinning during continental break-up. If the lithosphere on the flanks of a rift is already hot, then additional uplift from the lateral flow of heat from the rift would be obscured.

Cochran's model is fully analytical and can be evaluated quickly. For practical application to petroleum maturity, it is probably accurate enough because sedimentological effects, such as compaction and the subsequent change in thermal conductivity, give rise to greater uncertainties in palaeotemperature than do the simplifications of the model. Because the importance of slow rifting must be recognized, the industrial geologist should give careful attention to his seismic sections before applying Cochran's model. □

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Cell biology

Gel models for cell motility

from Harriet Harris

ACTIN filaments in many motile cells are randomly orientated in complex networks rather than in the parallel arrays of striated muscle, raising the question of how they participate in the organized movement of cells. The groundwork for attempting to answer that question was laid some years ago when it was demonstrated that soluble extracts of cells, prepared in the cold, formed gels on warming. Actin was a major component of the gels, some of which contracted in the presence of ATP, and myosin was identified in contracted material. However, crude gels may contain a bewildering assortment of components so it has been profitable to turn to reconstituted gels to test the effects of characterized proteins on actin behaviour. In particular, this allows the assessment of the combined effects of proteins which have such apparently opposing actions on actin as gelation and contraction. Two papers in the *Journal of Cell Biology* demonstrate the progress being made in the study of reconstituted gels from sea urchin eggs¹ and macrophages².

Macrophages contain a long flexible actin-binding protein (ABP) that cross-links actin filaments into gels³. If myosin is included with actin and ABP in the gels, they contract in an ATP-dependent manner; moreover, the effect of cross-linking the actin filaments with ABP is to lower substantially the amount of myosin required for contraction⁴. This is likely to resemble the physiological situation because, when phagocytic cells extend pseudopodia around a particle which is destined for ingestion, both myosin and ABP concentrate within the pseudopodia^{5,6}. A further degree of sophistication is imparted by the addition of macrophage gelsolin, a protein which solates actin gels in the presence of calcium ions⁷. When calcium is present it abolishes the amplifying effect of ABP on actomyosin contraction. In a gradient of calcium concentration, the gelsolin-containing gels contract away from the highest calcium concentration⁴; thus the ionic gradient imposes directionality on the movement of a randomly orientated macromolecular array.

A quantitative analysis of the structure of gels formed by the assembly of actin in the presence of ABP shows marked differences from networks of actin filaments alone²; the filaments are shorter and form a perpendicularly branching network, whereas free filaments cross each other at random angles. If the structural and mechanical properties of these gels can be correlated in detail, the properties of networks in cells may be deduced.

The popularity of sea urchin eggs for studies of cytoskeletal behaviour is largely

due to the substantial changes in actin organization that occur on fertilization: the cortical actin polymerizes^{8,9} and microvilli, containing cores of actin¹⁰ and fascin¹¹, form on the cell surface. Subsequently, cytoskeletal contraction occurs in the cleavage furrow during cell division. The questions posed by this system are, first, what are the precise changes in the structural organization of actin and, second, how are these changes regulated? To approach these problems Kane and colleagues have studied the gelation properties of sea urchin egg extracts. Upon warming, soluble extracts from unfertilized eggs form gels¹² which, if prepared under conditions such that the myosin remains active, contract in the presence of ATP¹³.

Recently Kane has prepared synthetic mixtures of purified components which form stable gels at low ATP concentration and contract when the ATP concentration is increased¹. The minimal requirements for such contractile gels are actin, cross-linking proteins and myosin. Superficially, therefore, both crude extracts and synthetic gels from sea urchin eggs appear analogous to their macrophage counterparts; the detailed organization of the actin filaments is, however, different. In the eggs, the cross-linking proteins are the 58,000-molecular-weight fascin and a 220,000-molecular-weight polypeptide. Fascin links the actin filaments into needle-like bundles, which are then linked into gels by the 220,000-molecular-weight component, which has no independent cross-linking effect on actin¹⁴. The gel thus consists of sets of actin bundles whereas the macrophage gel consists of separate filaments^{2,3}.

It is unclear whether this network of

bundles is a useful model for the organization of actin in the egg cortex. The behaviour of actin-fascin bundles in a network might be rather different from their physiological role in the cores of microvilli. The synthetic gels are also deficient in some important biochemical properties of the crude system; for example, fascin is excluded from crude gels upon contraction, but retained in synthetic actomyosin contraction. Until these points have been clarified, Kane's synthetic gels cannot be assumed to be a good model for sea urchin egg cortical actin. Nevertheless, they should provide a useful assay for additional regulatory components as these are found and purified.

An intriguing property of randomly ordered macromolecular systems is that directed movements may be brought about by directed stimuli. Examples are the response of macrophage gels to calcium gradients and sea urchin gels to ATP, but the scope could be broadened to include gels containing gradients of selected protein components. In this respect, the behaviour of gels may be seen as a direct contrast to that of muscle, in which directed movement is brought about by the action of a uniform stimulus on an ordered system of filaments. □

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Free-electron lasers

Past the visible light barrier

from C. R. Pidgeon

ALTHOUGH many experiments have successfully demonstrated the free-electron laser (FEL) as an amplifier of laser light, until a year ago the gain threshold for actual laser oscillation in a mirrored optical cavity had only twice been surpassed. A renewed burst of activity in the last twelve months has resulted in demonstrations of FEL oscillation in three new wavelength regions.

In a FEL amplifier, one observes or infers the amplification of an external laser beam as it interacts with an undulating electron beam passing through the periodic magnetostatic structure of a 'wiggler'. By contrast, a FEL oscillator produces a laser

beam without the need for an external laser. The spontaneous radiation generated by undulating electron bunches in the wiggler is reflected back and forth between a pair of end-mirrors, generating enough stimulated emission in successive electron bunches to produce and sustain a laser beam.

The first such FEL laser oscillator was reported by Deacon *et al.* (*Phys. Rev. Lett.* **38**, 891; 1977), who used the electron beam from a superconducting linac at Stanford University to produce infrared laser beams with wavelengths around 3 μm . Shortly thereafter, a Columbia University-Naval Research Laboratory collaboration

(Granatstein, V. L. *et al. Appl. Phys. Lett.* **30**, 384; 1977) used a pulsed-diode electron beam to achieve FEL oscillation at $400\text{ }\mu\text{m}$ in the far-infrared — a wavelength so long that lasing is facilitated by electron-electron plasma interactions that are not useful at short wavelengths.

The successful generation of a $0.65\text{-}\mu\text{m}$ FEL beam in 1983 at the French electron storage ring ACO was the first operation of a FEL oscillator at a wavelength in the visible region (Billardon, M. *et al. Phys. Rev. Lett.* **51**, 1652; 1983). Moreover, it was the first operation of a FEL using the circulating electron beam of a storage ring and the first to achieve laser oscillation with an 'optical klystron' — a modified wiggler design for enhancing the gain of FELs. Both were used because the FEL gain is drastically reduced at short wavelengths — crudely speaking it depends on the number of electrons per optical wavelength along the beam. Therefore to achieve the net gain required for oscillation (of $\sim 2 \times 10^{-4}$ per pass), it was necessary to go to the high current densities and low angular spread characteristic of storage rings and to use the optical klystron configuration: the three central periods were replaced by a three-pole dispersive section, strongly enhancing the optical bunching produced in the first section, thereby giving greater energy exchange (gain) between electrons and radiation field in the second undulator section. Typically, $75\text{ }\mu\text{W}$ average output power was obtained for a 2 kW intracavity peak power, giving 2.4×10^{-5} efficiency with respect to the total synchrotron radiation power. Tunability was shown to be limited only by the cavity mirror coatings, whose average reflectivity was at the technically available limit of 99.965 per cent. Higher ratios of gain to loss are expected from the use of better mirrors and smaller beam transverse dimensions.

More recently a laser oscillation at $11.6\text{ }\mu\text{m}$ in the near-infrared has been achieved by passing the electron beam of the Stanford superconducting linac through a tapered wiggler built at TRW, California (Edighoffer, J. *et al. Phys. Rev. Lett.* **52**, 344; 1984). The tapered wiggler configuration, in which the spacing between successively alternating magnet poles is gradually decreased towards the downstream end of the wiggler as the electron beam gives up energy to the radiation field, is the principle current approach towards the achievement of very-high-power, high-efficiency FELs in the near-infrared. To compensate for the average energy loss of the electrons to the optical wave, the magnetic field is made a function of the wiggler position, hence retaining a constant resonant condition for the output wavelength. The output power was reported as 4 W average or 1.2 MW peak (in a 4 ps micro-pulse) at $1.57\text{ }\mu\text{m}$, extracting energy from the electron beam in the tapered wiggler with an efficiency of better than 1.2 per cent.

Last November, the FEL at Los Alamos National Laboratory joined the small group of FELs that have achieved oscillation. During $70\text{ }\mu\text{s}$ pulses, 1 kW average output power was generated, which is reportedly a 100-fold improvement over previous experiments. By adjusting the electron energy the output wavelength was tuned over the range of $9\text{--}11\text{ }\mu\text{m}$ — the limits being set by the characteristics of dielectric-coated ZnSe mirrors. The FEL utilized a high-gain low-efficiency uniform wiggler. The efficiency of laser output to electron energy was about 0.25 per cent; small-signal gain was 15–20 per cent per pass.

There are hopes that tapered wiggler lasers will eventually operate with efficiencies closer to 20 per cent. But these high-power devices are probably too disruptive for storage ring beams. Restricted to linacs, they may be limited to infrared applications, though a tapered wiggler lasing in the visible is the goal of the radiofrequency linac development programme of the Math Sciences Northwest and Boeing groups. Clearly, efficiency is a much more important issue for the military and industrial uses of tapered wiggler FELs than it is in the use of visible and ultraviolet FELs, based on storage rings, for research purposes.

In the coming months we can expect a number of other FEL oscillators to become operational. In Britain, the UK FEL is a collaborative programme between Heriot Watt and Glasgow Universities and Daresbury Laboratory, based on the 30–150

MeV linac at the Kelvin Laboratory, Glasgow. The experiment is centred on $10\text{ }\mu\text{m}$, but a tuning of at least $2\text{--}20\text{ }\mu\text{m}$ is being investigated, with extension via harmonics to the visible range of the spectrum. This tunable high-intensity picosecond laser source is intended for research into fundamental properties of solids and molecular genes. A flexible high-gain uniform wiggler system, constructed from permanent magnet blocks, is enabling a thorough study of its operating parameters. A very similar programme is under way at CNEN (Atomic Energy), Frascati, using a 20 MeV microtron source, allowing FEL operation in the range $25\text{--}35\text{ }\mu\text{m}$ with a permanent magnet wiggler; at a later stage a new 30 MeV source will allow extension down to $10\text{ }\mu\text{m}$. Bell Telephone are using a 20 MeV commercial microtron in conjunction with a long helical magnet to give an output tunable from 100 to $400\text{ }\mu\text{m}$, dedicated to spectroscopic studies. The University of California at Santa Barbara hope to establish a user facility, based on an electrostatic accelerator, for far-infrared condensed matter studies with an average power of several kilowatts. Livermore are preparing to apply an alternative linac technology — the ETA and ATA high-current induction linacs — to the tapered wiggler FEL. Visible and UV storage ring experiments include those at Brookhaven and Frascati, and further extension to the extreme-UV down to $500\text{ }\text{\AA}$ at Stanford. □

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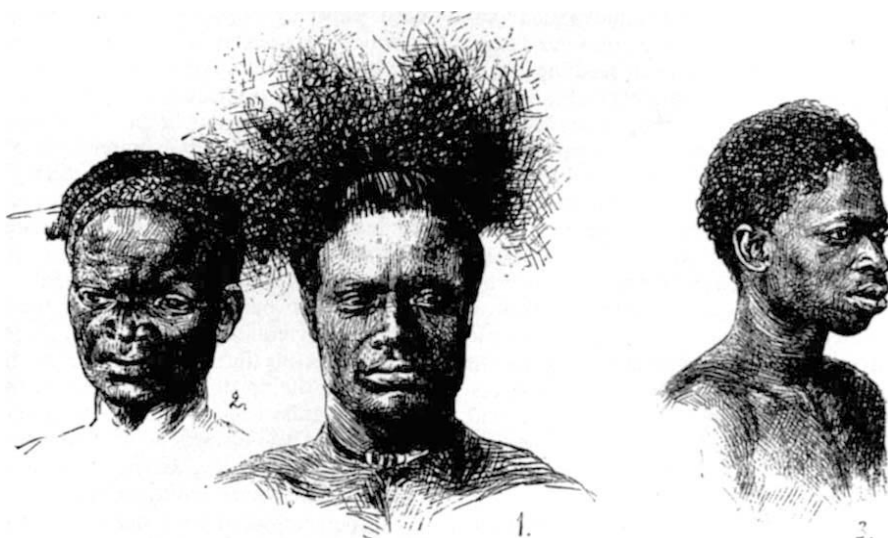


FIG. 3.—1, Mu-yansi; 2, Mu-téké; 3, Mu-shi-Kongo.

100 years ago

The River Congo, from its Mouth to Bólobó, by H. H. Johnston

ALTHOUGH claiming to be little more than the record of a passing visit paid to the Lower Congo Basin towards the end of the year 1882, this is really a work of permanent interest to the naturalist and ethnologist. The author, a young and ardent student of biology in its widest sense, here conveys his impressions of West African life and scenery in a series of graphic pictures, which owe much of their freshness and vigour to

the circumstance that they are always drawn at first hand from nature.

There is a deeply interesting chapter on the "People of the Congo". Here we find the Bantus as a race distinguished by a good observer, not only from the Hottentots, Hamites, and Negroes proper, but even from the surrounding Negroid populations. Further on the Bantus themselves are said to vary considerably in physical appearance, a statement fully borne out by the accompanying typical heads of a Mu-yansi, a Mu-téké, and a Mu-shi-Kongo (see Fig. 3).

From *Nature* **29**, 579, 17 April 1884.

Botany

Plants that track the Sun

from Harry Smith

THE facility with which heliotropic leaves and flowers turn to face the Sun has for so long been part of nature lore that it may well seem surprising to the casual observer that so little is known of the mechanisms of perception and response of foliar orientation. An even more puzzling problem of photoperception is posed by the so-called compass plants, whose leaves have a fixed orientation along the meridian. Our ignorance is particularly frustrating in view of the satisfying understanding of the ecological significance of these phenomena which has developed in recent years, as shown in a recent paper of Werk and Ehleringer¹. They analysed the behaviour of *Lactuca serriola*, a common weed whose cauline leaves have laminae facing east-west. The ecological advantage of this strategy seems to lie in the decreased light interception at the middle of the day, which reduces leaf surface temperature by as much as 5°C, a major factor in limiting water loss. Photosynthetic rates are high, however, in the morning and afternoon, when water relations are more favourable.

The opposite strategy — that of maximum interception of light — is favoured by plants whose leaves track the Sun with their laminae perpendicular to the direction of solar radiation. The increase in the daily rate of net photosynthesis due to such 'diaheliotropic' movements is considered to be of particular advantage in seedling establishment and for ephemeral or annual vegetation constrained to complete its life cycle quickly before the onset of long periods of drought or thermal stress^{2,3}. Ehleringer and Forseth⁴ recognized solar tracking in plants of 16 families growing in the arid regions of the southwestern United States, including both C3 and C4 species. In terms of total daily photosynthetic photon fluence, they estimated diaheliotropic leaves to be 38 per cent more effective in light interception than were fixed horizontal leaves, and an amazing 167 per cent more effective than non-tracking vertical leaves of random azimuth⁴. Relating these values of potential photosynthesis to actual productivity indicates that diaheliotropism increases carbon assimilation by at least 30–40 per cent, principally by enhancing photosynthetic rates in the morning and evening, when solar elevation is low and plant-water relations are favourable. An intriguing example of the ecological advantage of heliotropism occurs with certain flowers in which solar tracking elevates the temperature within the floral parts, producing 'solar furnaces' which aid both pollination and seed development^{5,6}.

The complement to diaheliotropism is paraheliotropism, in which leaf laminae are held parallel to the Sun's rays, ensuring

minimum absorption of radiant energy and consequent reduction of the heat load on the leaf with obvious benefits in times of water stress^{7,8}.

In contrast to the irreversible orientation of the leaves of compass plants — which is fixed during leaf development by a mechanism that seems to involve photoreception, since plants grown in the shade have randomly orientated leaves¹ — the leaf movement of heliotropic plants is reversible. Unlike stem phototropism, it is not the result of asymmetric growth; in most cases the movements are caused by specialized pulvinal — or 'hinge' — cells situated at the bases of leaves and/or leaflets, although some petioles appear to have pulvinal characteristics along most or part of their length. Changes in the ionic relationships between the pulvinal cells and their neighbours result in rapid spatial variations in turgor throughout the pulvinus region, causing movement of the dependent lamina⁹. The perception problem, therefore, becomes one of understanding how the direction of the Sun's rays incident upon the leaf is transduced into internal signals which regulate the ionic characteristics of specific pulvinal cells.

The general characteristics of diaheliotropic movements are well-defined in a recent paper by Vogelmann and Bjorn on *Lupinus succulentus*¹⁰. Typically, when they irradiated a leaf with a beam of white light directed obliquely at the upper surface, leaf movement began 30–60 min later, and reached a maximum rate of about 15° per hour. Importantly, irradiating the lower (abaxial) surface of the leaf caused no response. Using *Lavatera cretica*, Koller had previously shown experimental rates of movement of more than 90° per hour, far greater than the minimum required to track the Sun¹¹. It is also interesting that a beam directed from the base to the tip of the leaf causes it to rotate upwards, whilst the opposite orientation of the beam causes downward rotation; in both cases, the adaxial epidermis comes to lie perpendicular to the beam¹².

The perception of vectorial stimuli by plants is a particularly perplexing problem. Haupt and Feinleib have put forward two possible scenarios: either each sensor cell perceives the direction of the stimulus and the resultant intracellular gradients are integrated within the organ during transduction, or different sensor cells are stimulated differently because of the directional nature of the stimulus and the intercellular gradient is transduced to the orientation response¹³. For heliotropism it is not yet possible to distinguish between these two possibilities and a satisfactory hypothesis for vectorial photoperception does not exist.

To find even a promising idea it is necessary to go back 70 years to the work of Haberlandt¹⁴, who was far ahead of his time in so many fields of plant physiology. Studying the relationships between the structural anatomy of plant cells and their evident functions, he described the widespread occurrence of papillose epidermal cells — surface cells which are raised more-or-less into the shape of a dome but in which the inner walls are flat and parallel to the leaf surface. Such cells act as surface lenses and concentrate perpendicular light into a central illuminated zone of the inner wall, leaving the outer parts and the flanking walls comparatively dark. Haberlandt originally thought papillose epidermes concentrated light on to the photosynthetic mesophyll cells but later came to regard them as 'the optical sense-organs of foliage-leaves'¹⁴. By ingenious experiments on surgically removed epidermes he showed that bright spots could indeed be visualized in positions corresponding to the papillose cells, and he was even able to focus the image of a microscope stand using the particularly bulging cells of *Anthurium warocqueanum*. By wetting one portion of a heliotropic leaf with a thin film of water, separating it from the remaining dry portion by a black paper screen and exposing each to an oblique beam of light, Haberlandt showed that the leaf always orientated itself preferentially in response to the stimulus received by the dry region. This is exactly what would be predicted were the epidermal cells acting as condensing lenses. Oblique illumination of the epidermis results in a relative darkening of the central region of the inner wall and a relative brightening of part of the flanking regions — sufficient, perhaps, to establish the intracellular gradient which may be the prelude to the movement of the leaf. Little modern evidence on the epidermal anatomy of solar-tracking leaves appears to exist, although the prevalence of papillose epidermes in petals has been highlighted by Kay *et al.*¹⁵ who see their importance more in terms of light reflection than light perception. Perhaps a return to the ideas and methods of Haberlandt would prove illuminating, in more ways than one. □

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Virology

A new package for an old oncogene

from William D. Hardy Jr

PET cats develop retrovirus-induced lymphoid malignancies more frequently than any other mammal. The aetiological agent of feline lymphoid tumours is the feline leukaemia virus (FeLV), a highly contagious chronic leukaemia virus that induces both FeLV-positive and FeLV-negative lymphosarcomas. Like other chronic leukaemia viruses, and in contrast to acute leukaemia viruses, FeLV does not possess a transforming gene (oncogene) and induces leukaemia only after a long period of latency. But among the chronic leukaemia viruses of mammals, FeLV has a unique propensity to recombine with a variety of cellular sequences, thereby being converted into a variety of acute transforming feline sarcoma viruses distinguished by the oncogene they carry. Now, on pages 814, 853 and 856 of this issue of *Nature*, three independent groups report finding defective FeLV proviruses containing the *myc* oncogene in the DNA of 8 of 58 pet cats with naturally occurring FeLV-positive thymic lymphosarcomas and provide some evidence to suggest that a *myc*-containing leukaemia virus may be transmitted contagiously between cats¹⁻³. If so, it would provide the first example of a naturally occurring oncogene-carrying leukaemia virus of mammals.

All acute transforming sarcoma and leukaemia viruses have been identified and isolated by virtue of their ability to transform fibroblasts and/or haematopoietic cells in culture⁴. Since FeLV derived from feline lymphosarcomas does not transform cells *in vitro*, the three groups used *myc* probes and Southern blot analysis to study the cat *c-myc* locus in lymphosarcoma DNA¹⁻³. In order to show that the novel *myc* sequences found were encapsidated in functional viruses the Neil¹ and Mullins² groups inoculated feline embryo cells either with supernatant from cultured thymic lymphosarcoma cells or with blood plasma from cats with thymic lymphosarcomas. After inoculation the DNA of the embryo cells was extracted and digested with the restriction enzyme *Kpn*I. Since *myc* fragments of proviral origin can be distinguished from those of the cellular *myc* gene, it was possible to prove that the embryo-cell DNA contained *myc* sequences that were derived from viruses in the supernatants or plasma even though the cells showed no evidence of morphological transformation. This finding raises the possibility that *myc*-containing FeLVs may be transmitted contagiously among pet cats rather than generated *de novo* in each case.

It should be noted that the occurrence of *myc*-containing FeLVs varied markedly

between the three studies. Neil's group found evidence of *c-myc* alteration in four of nine naturally occurring FeLV-positive lymphosarcomas, in one of seven FeLV-negative lymphosarcomas, in two of three T-cell lymphosarcoma cell culture lines and in two of four experimentally induced thymic lymphosarcomas¹ whereas the Levy and Mullins groups, combined, found *myc*-containing proviruses in only three of sixty-one naturally occurring lymphosarcomas^{2,3}. These variations may represent the different extent of contagious spread of such viruses in Scotland¹ and the United States^{2,3}, or the selection of certain tumour types (thymic lymphosarcomas) by the Scottish group and not by the others.

Most naturally occurring leukaemias of animals are caused by contagiously transmitted chronic leukaemia viruses. Although the chronic leukaemia virus, avian leukaemia virus, induces bursal lymphomas in chickens via integration close to, and activation of, *c-myc*⁵ (which, in some way, leads to activation of a second oncogene, *B-lym*⁶), there is so far no evidence of oncogene activation by a chronic leukaemia virus in any naturally occurring mammalian leukaemia. In one mammal, the mouse, however, there is suggestive evidence of a related process in the form of *env* gene recombinant chronic leukaemia viruses. Three classes of murine leukaemia viruses (MuLV) can be distinguished on the basis of their host range in tissue culture which is determined by the viral *env* gene⁷. These are: ecotropic, which replicate only in murine cells; xenotropic, which replicate primarily in heterologous cells; and mink cytopathic focus-forming (MCF) viruses, which replicate in both murine and heterologous cells. MCF viruses are recombinants between ecotropic MuLV and endogenous *env* sequences related to xenotropic viruses^{8,9}. DNA of embryo AKR mice (high leukaemia strain) contains about 10 non-tandem copies of intact MCF-like *env* gene sequences with a proviral structure¹⁰. In spontaneous AKR thymic lymphosarcomas, these MCF-like *env* sequences are regularly found to have recombined with a specific region of the 3' end of the ecotropic *env* gene. This specific recombination appears to be the proximal event in the induction of AKR lymphomas and chronic viraemia is probably needed to generate the leukaemogenic MCF recombinant virus.

There is recent intriguing evidence for the existence of MCF-like *env* gene recombinant FeLVs. Elder and Mullins have shown a striking resemblance between the

nucleotide sequences of the envelope genes of subgroup FeLV-B and a Moloney virus-derived MuLV MCF virus¹¹. Both FeLV-B and MCF-MuLV can infect cells of various species, whereas FeLV-A and ecotropic MuLV usually only infect cat and mouse cells respectively. Cellular DNA of normal uninfected cats contains multiple copies of sequences that are related to the genome of contagious exogenous FeLV¹²⁻¹⁴, although these exogenous sequences cannot be induced to become infectious viral particles¹². Recently, the endogenous sequences have been shown to be significantly shorter than the exogenous infectious FeLV genome¹⁵ but with only a small deletion in the *env* region. It is possible that these endogenous *env* sequences may recombine with exogenous FeLV and form recombinant FeLV-*env* gene products. Recent data¹⁶ from this institute suggest recombination of that type as the best explanation for the presence of the FeLV-induced tumour-specific antigens on the cell surface of all feline lymphosarcomas¹⁷.

It is tempting to speculate that there may be a relationship between the generation of *env* gene recombinant FeLVs and oncogene activation. In this regard, Cloyd has found that lymphomagenic MCF viruses of thymic origin, AKR-247 and C58L1, replicate selectively in immature lymphocytes present only in the thymic cortex of mice¹⁸. One might postulate that similar *env* gene recombinant FeLVs infect only a subset of lymphocytes, those with specific receptors for the protein products of the recombinant genes, and that integration of the FeLV provirus in members of this subset might lead to leukaemogenesis by activation or alteration of *c-myc* or some other cellular oncogene. Further studies of FeLV-induced lymphoid tumours of pet cats may give us a clearer picture of the importance of oncogene-containing acute leukaemia viruses and *env* gene recombinant chronic leukaemia viruses in leukaemogenesis. □

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More numbers coincide

SIR — In the correspondence from Marcus Gossler¹ we are informed that, in the event of the statistical evidence being sufficient, “the numerological result has to be taken seriously and cannot be dismissed by any non-mathematical reasoning”. However, I think it also reasonable to point out (and I am sure all concerned would agree) that, although any such statistical evidence would undoubtedly give cause for the results to be taken seriously, any proof of *physical* significance can only rely on the verification of predictions arising from the said^{2,3} results.

I also think it reasonable to retract the statement, made in my article², that “I would state categorically that coincidence is ruled out”, as it is purely personal opinion and not based on any statistical analysis of the results. At the same time I would state my view that the commentary by John Maddox³ is also largely a matter of personal opinion, though its critical viewpoint was only to be expected in view of my “categorical” conclusions.

In the absence of any analysis of a verifiable statistical nature, my best defence lies in various new results I have produced. These undoubtedly increase the statistical evidence in favour of there being something to take seriously, although just exactly what that something is remains no less a mystery than in my original results. Perhaps it is best just to present the results and let readers decide for themselves.

My results are primarily based on a system in which the proton mass is represented as π^6 and the electron mass as $\pi/6$. One point worth bearing in mind (something I failed to raise in my article) is that $\pi/6$ is the volume of a sphere of unit diameter.

In these units I note that $M\mu$ = cube of harmonic mean of π and π^2 (1)

Result (1) is quite accurate, the values being 108.262 and 108.264 respectively.

It is obvious, of course, that the most hopeful candidates for significance are those results that are independent of any choice of mass units. One such result now follows and, paradoxically, it will be seen (from the next few results) that it does have a direct bearing on my choice of units.

Where R is the radius of a sphere whose volume is equal to the mass (in any units) of a particle (for example R_p is that radius for the proton, and R_{π^0} is that radius for the particle pi-zero).

$$\frac{4}{3}\pi(R_p - R_{\pi^0})^3 = \pi(R_{\pi^0})^3 = \frac{3}{4}M\pi^0 \quad (2)$$

The accuracy of result (2) is such that the left-hand expression (volume of a sphere of radius $R_p - R_{\pi^0}$) is just 1.0000059 times the two right-hand expressions.

Whatever one makes of results (1) and (2), I feel that there can be few critics who would not agree that the following result, in view of results (1) and (2), should provide (in the event of a statistical analysis) sufficient grounds for my “theory” to be

taken seriously.

$$\text{For a value of } \pi^6 \text{ for the proton mass,} \\ R_p - R_{\pi^0} = 2.9146418 \quad (3) \\ \text{harmonic mean of } \pi \text{ and } e = 2.9146474$$

There may be a connection between results (2) and (3) and

$$e^6 = \pi^5 + \pi^4 \quad (4)$$

The accuracy of this result is such that

$$e^6 - (\pi^5 + \pi^4) = 0.000017$$

Result (4) means that result (1) can be expressed as

$$M\mu = (2\pi^6/e^6)^3 \quad (5)$$

These are a few of the more interesting new results I have produced. Result (4) means that the array of powers of π in my article² can be expressed, fairly accurately, in terms of the value e as well as π . The above is not a full list of all those new results that I consider to provide the basis of the evidence in favour of my hypothesis being taken seriously, and I suggest that anyone wishing to know of the other results should contact me at the address given.

Even if one considers the evidence (which at this stage can only be of a statistical nature) to be sufficient, there remains the problem of the lack of any predictions arising from the results. I therefore have to be objective, and agree with John Maddox³ that it is one thing for the results to be “successful” (statistically) but quite another matter to prove that this success would make us “any wiser about the way matter is constituted”.

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Inverted logic

SIR — In his comment on perception of relief in micrographs (*Nature* 306, p.428; 1983), D.J. Cook has fallen victim to the very pitfall he sought to warn against. The replica image he describes as “correctly oriented” is upside down, and it is in fact his “inverted” picture which gives proper perception of relief. Topographical detail in micrographs of this type is “illuminated” not by light but by deposition of an electron-dense metal, usually platinum. In a standard photographic print, the custom is to orientate the picture with the direction of metal deposition from the bottom so that black deposits of metal lie below the protruding objects they pile up against, and white shadows are cast above them. The brain will then correctly perceive such objects as projections because it assumes the black deposits to be shadows cast by light from above. If a photographic reversal technique is used to produce a negative print, the white shadows cast by the metal can be turned into black ones. This then enables

the picture to be viewed as if illuminated by light, that is, with the direction of metal deposition from the top. In either type of photomicrograph, the key to correct orientation lies in knowing from which direction the metal was originally deposited. This is simply done by reference to in-built markers of known topography, for example, the particles that cover freeze-fractured membranes.

The “series of channels” described by Cook are, in reality, a network of ridges. They come from a tight junction viewed on the half-membrane sheet left attached to the cell’s protoplasm after splitting the membrane by freeze-fracture.

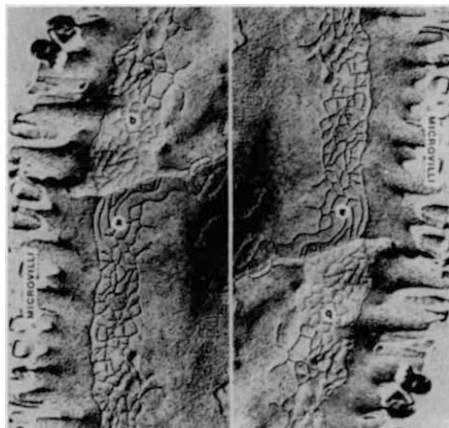
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● D.J. Cooke replies — I accept Dr Severs’ comments, which endorse my original point. Several times recently I have been misled or irritated because electron micrographs have been presented in such a way that the immediate percept of relief was incorrect. I therefore sent the letter in the hope that I could influence contributors to *Nature* to orient their electron micrographs in a “top lit” configuration which would elicit the correct perception of surface relief. I feel this would help those who read articles in *Nature* which include electron micrographs but who do not use electron microscopy themselves and I include myself in this category.

The illustration I used was not an original electron micrograph but from a book and was chosen as a good specimen of this particular relief reversal (channel to ridge and vice versa).

It now appears that I inadvertently chose a better example than I previously thought since the original publication was just such



an inverted image. My comments in the letter referred to the orientation as originally published, the left-hand photograph being the same as in the book, as can be seen from the lettering, while the right hand photograph corresponds to the book being inverted.

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Whigs and professionals

In recent years study of the history of science has been transformed. Colin Russell discusses the change in attitudes.

FOR most working scientists, excursions into the history of science are rather like eating Easter eggs: a harmless amusement, enjoyed by the very young and the very old, but strictly for holidays. Heroic tales from the past glories of science have long been deemed appropriate for youthful readers, and much history of science has been written by elderly, if not retired, scientists with half an eye on their own niche in the hall of fame. In fact both these characterizations of history of science — juvenile improvement or geriatric propaganda — are really caricatures. But if once they were partly true they are mercifully so no longer.

In the past 25 years or so, study of the history of science has changed out of all recognition. In a word it has been "professionalized". It is taught in several hundred universities in the Western world. A new breed of professionals, equally hungry for knowledge and anxious to display their skills, sustain a whole range of specialist journals and societies. Whatever be the causes (and they are complex), the professionalization of history of science and history of technology has not only given the subject its most substantial boost so far but has also posed new problems.

The raising of professional standards of scholarship really does mean that the "old" history of science is no longer adequate. It simply will not do, for instance, for books to be produced without references, adequate documentation or an index. Popular works that ignore such aids to the reader will have only the most limited value nowadays. Archimedes's bath, Newton's apple and Wöhler's destruction of vitalism are myths (and clichés) best forgotten in the light of modern scholarship. But these are relatively trivial matters. One of the rudest words which the new professionals love to apply to what they see as outmoded history of science is "Whiggish". To indicate the depth of opprobrium associated with this apparently mild epithet, let me give an example.

In 1899 one H.W. Picton published *The Story of Chemistry*, complete with a commendatory preface from Sir Henry Roscoe. Chemical history was divided into nine periods, the first four taking us up to the middle of the eighteenth century. The next three were: "The Childhood of Truth", "The Conflict with Error" and

"The Triumph of Truth". Picton saw chemical history as the inexorable, if gradual, conquest of error (which he called "mysticism") by truth. Those, like the phlogistonists, who opposed and retarded the emergence of the true oxygen theory of combustion, were given short shrift. The

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"Doctor Phlogiston, The Priestley politician or the Political Priest!" — Joseph Priestley in caricature (1791), a man in whom science, politics and religion were inextricably mixed.

fact that, at the time, they had the most cogent reasons for believing what they did is irrelevant. They were wrong — but only in the light of later research. Such history, written from the vantage point of modern science, offers no real insights as to why things happened as they did: it explores no intellectual culs-de-sac; worse still it makes no serious attempt to get inside the minds of those who were wrestling with most fiendishly complicated problems; and embedded within it is the unspoken assumption that truth will out some day, and that scientific progress is inevitable. In this respect its writers show a remarkable similarity to the Whig historians, who saw world history as leading to the ultimate

establishment and triumph of the British Empire.

Picton was quite typical of his time, and history of science still has its own brand of Whigs. These continue to present science in triumphalist terms, very flattering to the scientific community but curiously devoid of any inkling that science might — just might — be unable to control its own destiny and that of the human race. Was not a most successful television series entitled *The Ascent of Man*? Yet this was, as Professor S.L. Jaki has reminded us in *Angels, Apes and Men* (Sherwood Sugden, 1983), "an old shoe stitched together with Darwinian inconsistencies" (p.61).

Claiming to derive values from facts, it seemed blissfully unaware of the culturally generated assumptions in the mind of Darwin and his followers.

The difficulty, of course, is that in some respects the Whigs are perfectly right. The scientific method does, if properly applied, expose errors and lead to an ever greater apprehension of truth about nature. It is a very perverse historiography that ignores that fact. But it is equally perverse to imagine that the practitioners of science operate in a cultural vacuum. They, and we, are affected by the prevailing climate of opinion and this will have a profound effect on how science is perceived. Isaac Newton had only one head. The same brain which processed the theory of universal gravitation also preoccupied itself with matters of state, with personal problems in his family, with speculations about alchemy and with great issues of Biblical study and theology. It is foolish to imagine that Newton or anyone else could compartmentalize his intellectual life to such an extent that his science was completely autonomous. If we really want to understand how science developed we shall ignore its wider context at our peril. This is one pitfall mercilessly exposed by contemporary work in history of science.

In stepping gingerly round this one, however, we are in imminent danger of falling into another. Given that the

history of science can only be understood in a mature way by taking into account all kinds of other influences, the subject becomes fair game for those who have an ideological axe to grind, consciously or not. Thus some Victorian writers, intoxicated with the idea of progress and impressed by the filibustering of the established church in the wake of Darwinism, rewrote the history of science in terms of a conflict between science and religion, whose outcome was as inevitable as any good Whig could expect. One particularly notorious work of 1875, *History of the Conflict Between Religion and Science* by the American pioneer in photochemistry J.W. Draper, was still in print a year or two ago, as was its less vitri-

olic successor of 1895, *A History of the Warfare of Science with Theology* by A.D. White of Cornell. These books represent the fag-end of a tradition which, if no longer alive and kicking, is still able to display some vestigial traces of animation. Today historical justification for that position is amazingly hard to justify. It is widely accepted on all sides that, far from undermining it, science is deeply indebted to Christianity and has been so from at least the Scientific Revolution. Recent historical research has uncovered many unsuspected links between scientific enterprise and Biblical theology. The "conflict" model is not just a harmless anachronism. It is truth standing on its head.

Or again, an early Marxist view of Newton purported to explain his *Principia* largely in terms of social and economic forces. Since then various attempts have been made to reduce science to a social epiphenomenon and nothing more. Probably on account of their huge if unspoken assumptions, historical essays of this kind have not been conspicuously successful. Such crudities carry little weight today, yet they can remind us of more subtle ways in which our own presuppositions can nurture a distorted view of the history of science. In a recent lecture published in the *Times Higher Education Supplement* (2 March 1984), the Oxford historian of science, A.C. Crombie, has warned us against "politicized historiography" as fiction disguised as truth. Its ultimate condemnation is that it aims "to promote a party line . . . by exploiting the trust upon which a true republic of letters must rest". Whether this exploitation is from the political right or left it is also the republic of science which is in danger, and the threat must be taken seriously. Whether perfect objectivity can ever be obtained in science or history is another matter. But it's not a bad thing to aim for.

If modern history of science has exposed some of the old pitfalls in a new light it has also invented some of its own. Perhaps the most obvious transformation in recent years is that, in some areas, history of science is no longer fun. The feeling seems to be abroad that the hallmarks of scholarship must be an over-serious, if not pontifical, exposition. If the reader is bored out of his mind, that is his fault, not the author's. This is a great pity because many of the insights so painfully won and meticulously documented are of real importance for those who practise, teach or administer the sciences. Fortunately there are still many distinguished scholars whose lucid writings confound these criticisms and make excellent reading. But there are some who don't, and that is a pity.

Perhaps the biggest danger of professionalization lies in its exclusiveness. There is a tendency in some quarters to cultivate a language and style that is all very well in internal communications but not at all helpful if a wider audience is addressed. Articles replete with personalized

opinions, with footnotes longer than the text, with arcane references to "paradigms", "hegemony", "cultural legitimization" and so on cut little ice with those outside the favoured circle. Sadly, I can offer little encouragement to writers of such material that their work commands attention from the many active scientists who, nevertheless, may be quite interested in the origins of their subjects.

At a conference some years ago to celebrate the bicentenary of an important British scientist, papers were planned about his literary work, his reforming ideals, his public lectures, his institutional affiliations — even his sporting life! Only as an afterthought was anything proposed concerning his science, though that was the single reason for his importance. Instances like this can be multiplied. They arise when a rightful concern with the *context* of science has been extended to an almost monomaniac obsession, to the virtual exclusion of its *content*. The effect is simply to alienate large numbers of potential readers whose interest is primarily in the science itself. But does it matter?

Certainly it does. Science without its history is like a man without a memory. The results of such collective amnesia are dire. In chemistry, for instance, most of the great histories over the past 200 years were not written, as is often alleged, by chemists in their dotage, but rather in their prime of life. At least they thought historical studies conveyed some of that most desirable commodity "relevance". And so they do. They help us to understand something of the forces, internal and external, which fashion the shape of science, whether in the structure of scientific theories, the nature of experiments, the influence of religion or politics, the role of education and so on. They can save us from the bankruptcy of Whiggish triumphalism. They can add to our teaching a human dimension that can demonstrably reduce the alienation from science displayed by many young people in recent years. And, in rare cases, they can even assist us at the laboratory bench. Remember Lord Rayleigh and the inert gases?

The history of science was once conceived as part of science. Quite rightly, recent historians have come to see that it is also an important part of history. I believe that it is part of both. It has recently been argued that German history of science has failed to progress beyond narrow scientific confines, and to address itself to a wider audience of historians, sociologists and others. In the English-speaking world, however, we appear to suffer from the opposite malaise. So far has our pendulum swung towards history that we often fail to communicate with the world from which our subject sprang: the world of science itself. For historians to suppose that this does not matter would seem to imply a most curious evaluation of their own work. It almost suggests that modern science does

not *need* to take into account its origins and that it would have happened anyway. That is the most Whiggish philosophy of all! However, there are signs that a new synthesis is emerging and the reluctance to

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"Newton with his prism and silent face", the personification of scientific abstraction. The first seven words are those of William Wordsworth, describing the Roubilliac bust in Trinity College Cambridge.

consider issues internal to science itself is diminishing. In so far as this engages the interest of a new generation of potential scientists it is surely to be welcomed.

One of the most encouraging signs of renewed interest amongst scientists is the emergence of historical groups within the larger scientific societies. For some years such groups have existed for chemistry, astronomy and one or two other sciences. Now they are enjoying a new prosperity, and they are being joined by analogues in the life sciences, geology and other subjects. In my experience some of the most stimulating, enthusiastic and perceptive discussions in the history of science have taken place in such settings, both in Britain and elsewhere.

A recent celebration of the 250th anniversary of the birth of Joseph Priestley drew capacity audiences. They listened to historical papers ranging from Priestley as a victim of political caricature, through the relations between his theology and his chemistry, to the growth of pneumatic chemistry and the techniques available for gas analysis. This was in the middle of a highly technical, scientific conference. It is not in the least unique and is simply one illustration of two most desirable trends now discernible in the history of science: that it must be fully alive to the cultural context out of which science developed, and that it must also be earthed in the practice and theory of the science whose development it seeks to describe. □

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In between psychology

P.N. Johnson-Laird

In Search of Mind: Essays in Autobiography. By Jerome Bruner.
Harper & Row: 1984. Pp.306. \$19.25, £14.

THE imaginary line that divides the two cultures runs through the middle of psychology. On one side lies a science that aims to explain the mechanisms underlying behaviour and the mind. Its practitioners propose explicit theories, often modelled in the form of computer programs or axiomatized within a formal calculus, and attempt to test them in controlled experiments on human beings or animals. On the other side is a more diffuse and older subject, sometimes called "humanistic" psychology. It assumes that the most important aspects of mental life may not be open to scientific explanation. Its practitioners are committed to human values, to the "growth" of individual personalities, and to the healing of sick or disturbed minds.

For once, the grass looks paler on the other side of the fence. The scientists perceive their humanistic colleagues as idealistic and soft-headed social workers, whose ideas take far too much for granted, and who seem uninterested in submitting them to experimental test. The humanists see their opposite numbers as hard-nosed but short-sighted scientists wedded to the experimental investigation of trivial phenomena such as the distribution of reaction times to simple visual stimuli. In fact, the line of demarcation is not a sharp one, but a shifting boundary between two regions in imminent danger of total dislocation. What is remarkable about Jerome Bruner, the author and protagonist of this book, is that he straddles the divide.

Bruner tells the story of how a bright middle-class New York Jewish boy, who was blind for the first two years of his life, grew up to become a world-famous psychologist. His very first experiment was an unwitting childhood replication of Edmund Gosse's attempt to demonstrate the consequences of idolatry. Gosse knelt and worshipped a chair in the expectation of being on the receiving end of a thunderbolt. Bruner questioned the existence of God, and adopted a more direct procedure. In the middle of a thunderstorm, he challenged the Almighty to strike him down. Gosse reports that his religious faith survived unscathed but henceforth he put

less trust in the testimony of his father. Bruner with hindsight also offers a Freudian interpretation of his experiment, though it may be significant that he later ran into trouble at college for refusing to attend compulsory chapel.

Few people of Bruner's generation



probably set out to be psychologists. He tells us that he "landed in" the discipline because of the place (Duke University), the people (Berlin-trained Gestalt psychologists) and the times (the 1930s). The initial brush with Gestalt psychology contributed to his later success, because the United States was then dominated by the intellectual isolationism of the Behaviourists. They were so hard-headed about scientific psychology that they took the mind to be a ghost in the machine, which could be exorcised by the proper study of nerve, muscle and behaviour. Bruner never succumbed to Behaviourism, and he was to take a central part in the two major, and

related, revolutions in American psychology: the recovery of the mind as a respectable topic for scientific investigation, and the re-discovery of the role of unconscious mental processes.

Bruner began by setting a new fashion in the study of perception, the so-called "New Look". He and his colleagues carried out a series of experiments showing that people's desires, attitudes and expectations can affect the way they see the world. For example, children overestimate the size of coins, and children from poor homes make a greater error than those from affluent ones. Other studies showed that an emotionally charged word

sometimes takes very much longer to recognize than a more neutral word — as though the perceptual system defends the perceiver from the unpleasantness associated with the word. Such a result still strikes some psychologists as too paradoxical to be believed — how could a word be threatening unless it was recognized? — but it would hardly have surprised Helmholtz, who believed that perception was an unconscious process culminating in consciousness. The "New Look" gave rise to a long methodological wrangle, but it established Bruner's reputation. Never one to present a stationary target, he turned to the study of thinking, and started a new fashion for experiments on how people form concepts defined in terms of the conjunction or disjunction of properties. When he and George Miller set up the Harvard Center for Cognitive Studies at the beginning of the 1960s, the mind had finally been given back to American psychologists as a necessary topic for scientific investigation.

Despite his central role in these affairs, Bruner retains some scepticism about a full-blooded scientific approach. He writes:

I think I am suspicious of 'formal' models of human behaviour — theories couched exclusively in mathematical terms or in abstract 'flow diagrams'. I have always been sympathetic to the metaphors of computation and information processing, but resistant to getting trapped in their necessary measurement constraints. Perhaps I feel that such systems of measurement trap you on their flypaper while you are still wanting to fly. Their precision exacts a very high price in the abandonment of imagination...

Here, Bruner's insight into himself may have deserted him. It is a fallacy to assume that theories modelled in the form of computer programs demand any more precise constraints on empirical measurements than those couched in the vernacular. The real constraint of computer

programs is that they do not allow the theorist to take too much for granted; this constraint can liberate the imagination. The truth is that Bruner has no taste for this sort of theorizing, perhaps because he lacks the necessary background. Indeed, at one point, he refers to himself as a "non-scientist".

The danger of a dislocation between Bruner's scientific and humanistic tendencies reaches a maximum in his essay on consciousness. He distinguishes its evolutionary origin as a "tool" for solving problems from its "ornamental" role as a vehicle for "making visible the unseen, making possible the unimagined". He draws a parallel distinction between two modes of discourse — the formal scientific mode, and the narrative mode of the poet and myth-maker. The essay itself jumps from one mode to the other, its very form buckling under the pressure.

After the triumphs of the "New Look" and the study of thought, which were both to launch a thousand experiments into the literature, Bruner shifted his attention to schools, and to the reform of the curriculum. His best ideas were thwarted by politicians, but he nonetheless served to shape certain aspects of the educational system in the United States. Subsequently, he returned to the laboratory to investigate children's cognitive development. As he candidly admits, his work here was too close to Piaget's, and it was less well received. At the beginning of the 1970s after the Harvard Center had been disbanded, Bruner, always ready to move, came to England to the Watts professorship of psychology at Oxford. One of the most absorbing essays in the book describes his life in universities, and compares Harvard and Oxford to the latter's disadvantage. In retrospect, one can see that although the Oxford intellectual milieu suited him, the department of psychology did not. It lay entirely on the scientific side of the border, whereas he retained his scepticism. Ultimately, bored by "Bruner-bashing" seminars, he returned to the United States.

Although Bruner has written a number of widely praised books, this one is his best. Its success rests on two factors. One is Bruner's talent for being at the centre of the cognitive revolution. The other is his skill in re-creating on paper his own personality and cast of mind — a vivid, and very unEnglish mixture of passion, restlessness, gregariousness and intellectuality. He is indeed an intellectual first, a psychologist second and a scientist third. His book is bound to be widely read by psychologists; it should be read by anyone who wants to understand what has happened to American psychology in the past half century. □

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Through to another dimension

Thomas Banchoff

The Planiverse: Computer Contact with a Two-Dimensional World.

By A. K. Dewdney.

Poseidon, New York: 1984. Pp.267.

Hbk \$16.95, pbk \$9.95. To be published in the UK on 11 May by Picador, hbk £7.95, pbk £2.95.

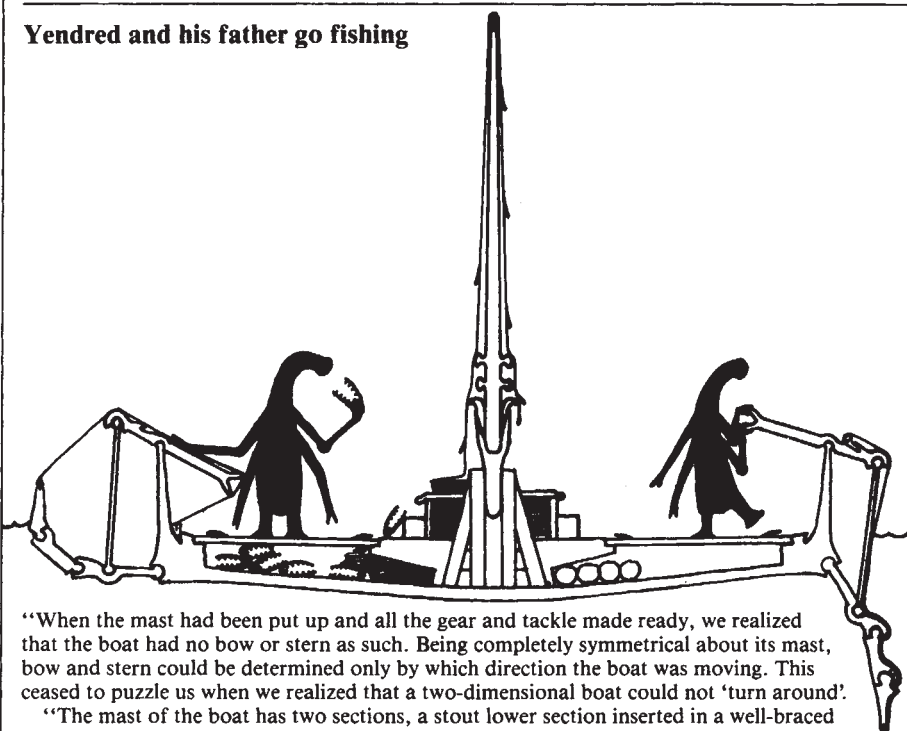
ONE hundred years ago *Nature* published a review of *Flatland: A Romance of Many Dimensions*, Edwin Abbott Abbott's classic tale of A Square, a two-dimensional creature who encounters a visitor from the third dimension. Now there appears a new book, *The Planiverse* by Alexander Keewatin Dewdney, hailed by the publishers as a worthy successor to *Flatland*. For those of us who received our first challenge to think about lower and higher dimensions from Abbott's little volume, this claim must be viewed with scepticism. Yet the claim is correct.

Dewdney's volume is a fable for our own time that will delight anyone who likes a good story and who enjoys a mind-stretching experience. Subtitled *Computer Contact with a Two-Dimensional World*, the book introduces us to "Yndrd" (Yendred), a creature we meet only on the

video screen of a professor of computer science, Dewdney himself, and his team of students. The progressive encounters which intermesh the world of the observers and the world of the observed lead to an amazingly rich description of Arde, a two-dimensional planet, complete with a well-developed technological society, worked out in fascinating detail. But this is no video game and still less a dry treatise on two-dimensional science. It is simultaneously a fine tale of adventure, as we accompany Yendred on his trek in search of higher meaning for existence, and the story of Dewdney and his students as they become caught up in the experience and are themselves educated through their contact with Arde.

The original reviewer of *Flatland* found some parts of the book tedious, as A Square went on at length about the physiology and psychology of perception, or described his society's blinkered view of women's education (an effective satirical device by Abbott, a distinguished schoolmaster well known for his liberal leadership in the cause of education for women). Similarly some readers of *The Planiverse* will find parts of it slow going, even though the author has relegated many technical asides to special boxes or to an appendix. Yet the pace of the book gives assurance that each new chapter will present something quite different, as the author strives to include material of interest to a wide range of readers — biology, astronomy,

Yendred and his father go fishing



"When the mast had been put up and all the gear and tackle made ready, we realized that the boat had no bow or stern as such. Being completely symmetrical about its mast, bow and stern could be determined only by which direction the boat was moving. This ceased to puzzle us when we realized that a two-dimensional boat could not 'turn around'.

"The mast of the boat has two sections, a stout lower section inserted in a well-braced framework, and a graceful upper section resting on this and held in place by two wedges or pegs. Two long ropes dangled from the top of the mast. There were lockers for food, tackle, and line, as well as two holds for the catch. At either end of the boat were oars. One of these was soon being pumped by Yendred's father; the other was folded up to be used by Yendred on their return. Ingeniously designed, the blades of the oars were hinged so that when the rower pulled down on the handle and the blades stroked toward the rear, they formed a rigid paddle. When the rower pushed up on the handle, the blades moved forward, folding out of the way so as not to counteract the boat's forward motion." (From *The Planiverse*.)

sociology, physics, art, engineering, religion, on and on.

Indeed, when earlier work on a plane world was reported by Martin Gardner in *Scientific American* in 1980, Dewdney received over one thousand letters so there is no lack of enthusiasm for the subject. What is exceptional about the present book is that it brings all of us in to share the excitement of discovery of this new land.

When *Flatland* first appeared, some readers were disappointed that the author did not consider in more detail the physical laws which govern such a two-dimensional world. A contemporary of Abbott, Charles Howard Hinton, published *A Plane World* in 1884 and later his own *An Episode of Flatland* in 1907, trying in each to work out the scientific and technological implications of planar existence. Dewdney's book is more a successor to Hinton's work than Abbott's, although some of the basic issues concerning artificial intelligence, and the interaction of the observer and the observed, parallel a number of the key questions in *Flatland*. *The Planiverse*, too, lacks explanation at crucial points. The mechanism by which the original contact is established and maintained is certainly mysterious; the technique of "eaves-dropping", though effective in moving the story along, seems far fetched; and the description of perspective and ambiguity seems to ignore the fact that Ardeans are functionally binocular, at least when they turn their heads. It seems certain that the author will receive a great many more letters from readers who become intrigued by this enterprise.

Names can also be a distraction. In *Flatland* Abbott used "A Square" and "The Chief Circle" while Hinton's all-too-human protagonists were "Laura Cartwright" and "Harold Wall". Dewdney's creatures have unpronounceably exotic names — Tba Kryd, Kewbt and so on — and they speak with a syntax reminiscent of that of Yoda in *The Empire Strikes Back*. It is difficult, apparently, to find a middle ground.

But these points will not distract a reader who becomes gripped by the tale. The ending leaves us wanting more, and not fully understanding what we have experienced. At the conclusion of *Flatland*, the hapless narrator, A Square, in the cell where he has been imprisoned for his unorthodox higher-dimensional views, wonders if it has all been but the fabric of a dream. Dewdney and his students at least have one another, but they too have to face the insubstantial fading away of their contact with Arde as the image of Yendred disappears from their screen.

Flatland is more alive than ever after one hundred years. *The Planiverse* will take its place alongside that book as a worthy companion, treating us all to the challenge of other dimensions. □

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Among the shifting sands: science in its place

David Bohm

Critique of Scientific Reason.

By Kurt Hübner. Translated by Paul R.

Dixon Jr and Hollis M. Dixon.

University of Chicago Press: 1983.

Pp.283. \$27.50, £22.

FOR several hundred years, scientific modes of reasoning have generally been taken as the proper forms for the expression of knowledge, not only in science but in most other areas of study. In this book, Professor Hübner makes an important contribution to the growing questioning of science as a unique road to truth. By showing how science is a special case within the larger sphere of human cognition, he not only brings out the limitations of scientific thinking but at the same time clarifies the basis on which such thinking is able to take place.

Hübner begins by criticizing Kant's notion that *a priori* categories, such as causality and reciprocity, present us with the necessary framework within which any experience at all is possible. He illustrates his point with quantum mechanics as a case study. In doing this, he cites the Bohr-Heisenberg approach, in which the quantum theory permits only transformations from statements concerning observables to other such statements without giving any notion as to how these transformations came about and as to what were their causes. This approach is then contrasted with my own proposals, made in 1951, of an alternative interpretation of the theory, in which the transformations could in principle be followed in detail and explained causally. From the possibility of having these two different interpretations in the same theoretical domain, it follows that neither the notion of causal principle nor that of an acausal principle is actually inherent in what is. To assert either causality or acausality as a principle of *unlimited* validity is therefore not justifiable. Rather, each of these positions is a methodological postulate, and considerations beyond those of scientific fact and theory are what actually make possible a decision between these alternatives, at any particular stage in the development of a science.

I would like to remark in passing that I think that Hübner is right on this point. (Indeed, I did put my own views rather dogmatically, but only at the beginning. Since then I have suggested that we use *both* interpretations to obtain a greater insight into the meaning of the quantum theory than is possible with one of them alone — see D. Bohm and B.J. Hiley *Foundations of Physics* 12, 1001; 1982).

Professor Hübner then goes on to

generalize these conclusions. He criticizes the notion of *facts* that stand by themselves and shows that they all depend crucially on what he calls systems-ensembles. Such systems-ensembles are characterized by certain kinds of presuppositions, which he terms precepts. These are contained not only as tacit assumptions of the theories under consideration, but also as a wide range of additional theoretical precepts, such as those having to do with the functioning of measuring apparatus and the allowable procedures for collecting and admitting data. Even more important are the axiomatic principles (e.g. Euclidean geometry), judicative precepts (i.e. rules for accepting or rejecting theories) and normative precepts (such as causality or non-causality). These all have a certain *a priori* character, and yet they differ from Kant's notion of a fixed and universal *a priori*, in that it is the *historical* context that determines them. As knowledge develops these precepts are therefore constantly changing. At first, this change merely *explicitates* what is implicit in the overall structure of ideas. But from time to time, the entire system-ensemble undergoes a radical *mutation* (corresponding to what Kuhn calls a scientific revolution). In this process, there is no fixed and final truth that is being approached. After a long time, the systems-ensemble changes so much that what was recognized as a fact in an earlier system often has no place in the later system. Thus, mediaeval alchemical facts, based on the accepted precepts of the time, have, for the most part, no place in physics and chemistry. We may expect that, in a century or two, precepts may have changed so much that many of our own present-day facts will also have little or no place in the thinking of that time.

Clearly, Hübner is here criticizing Karl Popper, who, he asserts, is leaving out the whole body of historically grounded precepts which Popper tacitly takes for granted in his attacks on historicism. Hübner further points out that, indeed, no theory can be falsified (or verified) except within such a system of historically based precepts.

Hübner is not denying the role of the actual experimental results and the creative insights of scientists, as they try to deal with contradictions, within the particular systems-ensemble in which they are working. Rather, he emphasizes that even these experimental results and creative insights have to work in a context that is determined by the total set of historically developed precepts that are part of the general background of scientific thought of a given time.

He then extends these notions to historical science and shows that, at bottom, it is also based on sets of facts and insights growing in a context of historically developed precepts. This argument leads in to a comparison of the modern scientific and technological systems — ensembles of precepts, and those prevailing at a much

earlier time when mythological precepts held sway. Hübner makes it clear that in those times the fact itself was expressed in terms of mythological precepts, and so was experienced in a very different way to that which is now common (e.g. art and the sacred were sensed as one and indivisible). This account of the nature of the difference is such that I, for one, was able for the first time to appreciate the significance of the mythological approach to life as a whole, and to see that within it everything is at least as consistent as it is in our approach through science and technology.

Of course, Hübner does not expect us to return to a mythological world. However, he does suggest that sooner or later the world of science and technology will have to give way to a new world with a very different system-ensemble of precept. In this way, he indicates that the problems of our present scientific and technological world (e.g. pollution, destruction of the environment, creation of a meaningless way of life and so on) may dissolve away. On the other hand, within our own system, it is by now becoming evident that these problems cannot really be solved in any fundamental sense.

Thus far I have dealt with only some of the main points treated in the book. There are further important criticisms of a number of scientific and philosophical theories in it, as well as a carefully developed historical account of how Kepler came to discover his elliptical orbits. This account not only illustrates Hübner's theses concerning the role of systems-ensembles. It also serves to raise the point that had Kepler followed Popper's judicious precepts on falsifiability, he would have dropped his work long before it could have reached a successful conclusion. Thus, he argues, Popper's falsifiability criterion cannot be universally valid.

Critique of Scientific Reason makes a new and original contribution to the understanding of how the development of knowledge actually takes place. Doubtless, though, it contains features that can be criticized. For example, while Hübner claims that his own ideas are not inseparably based on precepts (as yet unstated), it is by no means clear this is actually the case. It is to be expected that some of those who have been criticized by Hübner will make rejoinders that further serve to show the limits of his work. For the present, I would only add that just because it shows the boundaries of scientific reason, his approach tends to make scientific research seem less significant and thus may tend to damp the passion needed for great and original scientific discoveries. Nevertheless, it must be said that on the whole this book deserves very serious consideration, especially by scientists and philosophers. □

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Concepts of quantum theory

Hans Primas

Quantum Theory and Measurement.

Edited by John Archibald Wheeler and Wojciech Hubert Zurek.

Princeton University Press: 1984. Pp.811. Hbk \$75, £69.30; pbk \$19.50, £13.90.

WHAT is quantum mechanics about? Is it about individual systems or about statistical ensembles? Is it about objectively existing entities, or about the results of measurements or about the sensations of the observers?

There is no general agreement, and a reference book containing the most important papers on the conceptual problems of the subject has been needed for a long time. In *Quantum Theory and Measurement*, John Wheeler and Wojciech Zurek have tried to satisfy this need. They have selected forty-nine papers to illuminate the meaning of quantum theory as it is disclosed in the measurement process, among them the key papers of the magnificent Bohr-Einstein dialogue, the famous paper by Einstein, Podolsky and Rosen, and Schrödinger's cat paradox (in an English translation). Most welcome are the hitherto unpublished lecture notes by Eugene Wigner on the interpretation of quantum mechanics, as well as a translation of London and Bauer's classic "The Theory of Observation in Quantum Mechanics". A pleasant surprise are the papers stressing the engineering aspects of quantum measurements, specifically dealing with optical channels, quantum noise and non-demolition measurements.

Why is the theory of measurements in quantum theory so controversial? Perhaps it is because our textbooks have uncritically adopted the pragmatic rules that working physicists required in the hectic time around 1928 in order to be able to use the new but yet incompletely developed quantum mechanics. In 1927, John von Neumann formalized not only the unitary time evolution given by the Schrödinger equation but also a second kind of state change which he supposed to occur during a measurement. This so-called projection postulate involves a projection of the state vector onto a subspace determined by the outcome of the measurement and is commonly referred to as the "collapse of the wave packet". Within the traditional formalism this collapse of the wave packet cannot be described by the Schrödinger equation. This situation gave rise to severe philosophical disagreements and wild speculations. Even mind and consciousness have been evoked as a way out of the alleged paradoxes of quantum measurements. Since the view that quantum events do not exist in the absence of some observing mind is not to everybody's

liking, many disquieted physicists abandoned the view that the task of science is to describe nature. One formally admissible but rather cheap way out of this dilemma is to adopt a very narrow-minded positivistic or operationalistic viewpoint, claiming that all a theory can do is to describe and predict the results of measurements (that is, to adopt an "epistemic interpretation"). From this point of view the state vector is just a calculational tool, it does not represent reality. In its most extreme variant, the referent of the theory is the mind of the observer.

All the so-called paradoxes of quantum measurements depend crucially on the fiction of a "measurement of the first kind" (a measurement which is supposed to be instantaneous, repeatable and give sharp values). Faced with the strange consequences of the projection postulate, it is astonishing that so often the existence of measurements of the first kind is taken for granted. All actual measuring processes we really understand today (nuclear magnetic resonance experiments, for example), are certainly not measurements of this type, and they can be discussed without the projection postulate. In contradistinction, a full theoretical account of the traditional two-slit experiment is extremely complicated and out of the reach of our present abilities. Its consideration in terms of the collapse of the wave packet has only the status of a rule of thumb which should not be taken too seriously.

As to this book, it is in my view most unfortunate that the editors have not concerned themselves with modern developments. Obvious omissions are the proof that in quantum mechanics repeatable measurements can only exist for observables with a discrete spectrum (that is, the projection postulate is irrelevant for the most important observables; Davies and Lewis, 1970; Srinivas, 1980); Holevo's discussion of optimal quantum measurements (solving the old problems of the joint measurement of incompatible observables and the measurement of the time parameter); the generalization of the unitary time evolution to completely positive dynamical semigroups (which settles many questions of irreversibility in quantum mechanics); and the logical possibility that the referent of quantum mechanics is objectively existing individual systems (i.e. an "ontic interpretation" in the sense of Scheibe, 1964).

Every theoretical discussion of a realistic laboratory experiment is a difficult undertaking. An axiomatic approach starting with some postulates about measurements (such as von Neumann's projection postulate) can never do justice to the complex nature of actual experiments. From a modern point of view, the measurement problem of quantum mechanics is a problem of the interaction of quantum systems with classical systems. A classical system is characterized by a Boolean logical

structure (or, equivalently, by a commutative algebra of observables). The essential difference between classical systems and quantum systems is not the occurrence of Planck's constant of action (classical systems may very well depend on Planck's constant) but the fact that quantum systems are entangled by Einstein-Podolsky-Rosen correlations. This holistic feature of quantum mechanics may be difficult to grasp for a scientist educated in the classical Cartesian tradition. Thirteen well-selected papers of this collection document the experimental reality of the holistic non-separability of quantum systems.

In order to understand measurements, we must understand the existence of classical subsystems in a quantum world. That is the main problem and a tough one. If it is solved, a measurement can be described by a channel (in the sense of Umegaki) which transfers the state of the quantum object to a state of the classical output system. Much research in this field has been done in the past decades and many new important results are known. None of them is mentioned in the book. Equally disappointing are the commentaries. For example, in their "Guide to Some Further Literature" the editors say that Gleason's theorem "simplified the axiomatics of quantum mechanics". Such a phrasing is grossly misleading: Gleason's theorem is a conceptually important result explaining why linear functionals can be used to

describe quantum states. Another example of the editors' disregard of present research is to do with the irreversible behaviour of some quantum systems. The reprinted papers deal with ergodic properties and are certainly of historic interest, but helpful comments are lacking. I think it should have been the editors' duty to inform the non-specialist why ergodic properties alone are irrelevant and why one has to require stronger mixing properties.

In an anthology of this sort, some arbitrary decisions are unavoidable. But still it is hard to understand why the editors decided not to reproduce the thoughtful and masterly "Quantum Physics and Philosophy, Causality and Complementarity" by Bohr (1958) and "On the Interpretation of Quantum Mechanics" by Fock (1957).

Although the many omissions may be regretted, this set of papers makes fascinating reading. The editors expect that their collection can be used as a source book for a seminar on the subject. The historical aspects are certainly well covered so it is, indeed, an obvious starting point for those entering the field. But it far from represents the state of the art, and no reader should suppose that the book will allow him to catch up with modern developments. □

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Mechanics of physics

Abraham Pais

The Quantum World.

By J.C. Polkinghorne.

Longman: 1984. Pp.100. Hbk £7.95, \$14.95.

THE Curate of St Michael and All Angels in Bedminster is an interesting man. He knows that "science has achieved its success by restricting itself to a certain type of inquiry", and he was elected FRS for contributing to this success. He knows too that there are other issues which are essential for a grasp of our World but which are beyond the ken of science. "God is not to be put to the test."

These sayings of the Curate, culled from his recent article in the London *Times*, made me turn to his new book, *The Quantum World*, with the confidence that it would not serve up that blend of the material and the mystic which of late seems so palatable to so many. I was not disappointed. This book is short and lucid. It demands thinking but no knowledge of higher mathematics. Its language is simple. Having been reared on the principle that it is not nice to use eight-letter words in public, I am happy to report that the word ontology occurs only once. Formulae are

given here and there but mainly to show what they look like. Nine brief appendices introduce the reader to more arcane subjects including a half-page derivation of John Bell's celebrated criterion for the validity of quantum mechanics which has recently been subjected to stringent laboratory tests. (No surprises: quantum mechanics works.) A helpful glossary is also included. Princes and Poppers alike will derive benefit from this handsomely produced volume.

"Professional practitioners of quantum mechanics can calculate away without worrying about the outcome of the debates about the foundations of their subject" (p.16) which centre on the question: is it necessary to include a specification of the experimental arrangement in defining what we mean by a physical phenomenon? "No", says the classical mechanic who uses the code words: objective reality. "Yes", says the quantum mechanic whose code word is complementarity and who bases his argument on the ineluctable indeterminacy principle. After giving a clear account of the transition from the classical to the quantum era, the author guides us through the quantum arguments by the fitting device of a tour through thought experiments which illuminate this subtle issue. One such experiment is that of Einstein, Podolsky and Rosen. I regret that the author follows others by referring to the

EPR result as a paradox. The EPR paper, logically impeccable, merely shows that objective reality and complementarity cannot both be true. Einstein never called it a paradox. Nor was he "wistful[ly] longing after a determinate hidden variable theory" (p.73). He never referred to "hidden variables" in his writings and in fact often called them a cheap way out.

In addressing these questions of principle, care with language is of the essence. I cannot subscribe to the author's statement (p.60): "Measurement involves an intervention by our everyday world into



John Polkinghorne — "testimony to the fact that physics is necessary but not sufficient for salvation, that science and religion can coexist in harmonious complementarity".

the quantum world". I would rather say with Bohr: "There is no quantum world . . . It is wrong to think that the task of physics is to find out how nature *is*" (p.79). May we then not ask what the World *is*? Of course we may, but here physics "restricting itself to a certain type of inquiry" cannot give answers. The author's life as well as his *oeuvre*, especially this lovely little book, bear testimony to the fact that physics is necessary but not sufficient for salvation, that science and religion can coexist in harmonious complementarity. He would agree, I think, with the quantum mechanic's reply to Einstein's assertion that God does not play dice: how do you know? □

Abraham Pais is Professor of Physics at the Rockefeller University, New York. His biography of Albert Einstein, 'Subtle is the Lord . . .', first published in 1982, has recently been issued in paperback by Oxford University Press.

Cockcroft: a novel perspective

William Cooper

Cockcroft and the Atom.

By Guy Hartcup and T.E. Allibone.

Adam Hilger, Bristol/Heyden, Philadelphia: 1984. Pp.320. £18.95, \$34.

SINCE the title of Hartcup and Allibone's book may sound a bit vague, perhaps I should begin by saying what *Cockcroft and the Atom* is about. It does not set up — as it seems to me — to be a full-dress biography of John Cockcroft (1897–1967), or a history of atomic science during the first half of the twentieth century; rather to be planned as a sort of documentary about the context of events in which Cockcroft's life, as scientist and man of affairs, was central, of events in the world of atomic physics that he influenced or that influenced him.

Does the plan succeed? For most readers I imagine the answer will be a straight "yes": for myself, some mild reservations. The book has been extensively "researched", as it is now called — records have been consulted, letters read, people interviewed; the facts laid end-to-end in chronological order. "A comprehensive compilation" is the phrase that springs to mind. (The mother-and-father of the comprehensive compilation is of course the computer.) Every event is noted, every participant named. Speaking as a novelist — and why not, if there is a fresh view to be added thereby? — I find something Zola-esque about the authors' naturalistic piling on of detail, maintaining throughout exactly the same degree of detail: what I miss is Zola-esque art; that is to say, in down-to-earth terms, an author's personal voice sounding through, an author's personal intelligence commenting and interpreting, an author's personal literary talent — the things that make one want to read a book for *itself*, as well as for the information it contains.

I don't doubt that many readers will feel I'm asking too much: out of 100 ears on which my mild strictures fall, 98 will probably be deaf to them. Just as well, perhaps, since the comprehensive compilation is with us, and will be so to an increasing extent. (Yesterday a youthful American pupil of mine said to me enthusiastically: "The word-processor makes writing so *easy*!" Just so.) However — to be fair — one can't help but feel that all the facts are there. Yet on some pages there are as many as a dozen names, normally far too many for comfortable reading. Comfortable enough for me in this case, because often half of them were of men I'd come across myself in my time; but for the comfort of other readers I'm not so sure. All the

same, when it's compiled as successfully as this one, the comprehensive compilation undeniably earns its place in the library.

I was an admirer of Cockcroft, a fine, stocky, sensible, cautious Yorkshireman, who indulged in a minimum of speech and in practically no change of facial expression. (That expression was nevertheless amiable, thoughtful, smiling.) If one addressed a remark to him, it was only when, after the ensuing silence, he either took the famous black notebook out of his pocket or actually said something, that one knew for certain that he'd heard. It gave me lasting pleasure to think that at a dinner-party in his house I'd made him burst into laughter — till I saw in this book a photograph of him laughing with George

what was in the sheer physics of it an absolutely fundamental discovery. The authors of this book take in their stride Cockcroft and Walton's being made to wait so long — *theirs* not to reason why, they say. But what about *ours*? Did it take the Nobel committee nineteen years to recognize the experiment as breaking open an entirely new line of powerful experiments to be made with particle-accelerators? Or did it take those members who opposed the award all that time to disappear from the scene? Or what? *Someone* must know. *There's* a fascinating detail I should really like to be told.

Chadwick, speaking clearly for the "physics-is-physics" school, said of Cockcroft:

For example, his knowledge is wide but it is not at all profound; his views are of rather a dull everyday hue. On the other hand his temper is so equable and his patience and persistence so inexhaustible that we can put in lively and relatively irresponsible men who have the real feeling for research without fear of upsetting the balance.

I sense a pleasing Jane Austen-ish snobbery about the physics-is-physics school to which Cockcroft was neither born nor bred. He was an *applied physicist*. Between leaving school and turning up at Cambridge in 1922 to read for the Mathematical Tripos, he had taken a mathematics degree at Manchester University, served as a signaller in the trenches at Passchendaele, returned to Manchester Tech to take a degree in electrical engineering while doing a Metro-Vick apprenticeship. Yet how right Chadwick's intimations turned out to be, of what Cockcroft could be entrusted with, both inside and outside the world of physics — spending the early years of the Second World War on the vital practicalities of radar; then taking over the wartime atomic scientists' team in Montreal and Chalk River; then coming back to run them in Harwell, each team having its contingent of "lively men with a real feeling for research". (As I was party to appointing many of the Harwell contingent, I should be the last person to say any of them were "relatively irresponsible".)

"Without upsetting balance." That exactly describes Cockcroft's reign at Harwell from 1946 to 1958, during which he directed some of its most important research: he may have been neither a super administrator nor a born manager — but the place *balanced*.

The authors observe that Cockcroft had his failures and disappointments, made his mistakes. He made a mistake — astonishingly against caution — with his optimism about the experiments aimed at generating power from fusion. And his private hopes of going back to his old college, St John's, Cambridge, were dashed when, in a magisterial election which reminded him and his wife of C.P. Snow's *The Masters*, the Fellows elected

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The Cockcroft-Walton accelerator, April 1932, with Ernest Walton seated to observe the scintillations.

Gamow. Well, Gamow was a funny man.

It was a theoretical memorandum of Gamow's which sowed the seed of the Cockcroft-Walton "atom-splitting" experiment, the first of its kind, in 1932. Cockcroft cottoned on to what Gamow was saying about bombarding elements with protons, and he addressed to Rutherford a calculation (reproduced in this book) that led to the famous experiment being set up. Then something odd happened. Using a lithium target bombarded with a beam of protons, Cockcroft and Walton began by looking for gamma-rays; and it was when Rutherford, fed up with their getting no results for a couple of years from their electroscopes, told them to install fluorescent screens, that they promptly picked up the alpha-particles into which the lithium atoms had been split; a prime experiment, for which the two of them were awarded a Nobel prize for physics — *nineteen years later*. James Chadwick, for discovering the neutron at about the same time got his Nobel in three years — very properly, for he had made

the Senior Tutor, and not Cockcroft, to be their Master. The upshot was a turn in his career, a definitive turn to Whitehall and national affairs. It is interesting to speculate whether, if he had gone back to Cambridge then, he would have played a comparable part in first national and later international affairs (though in a less definitive way he was already embarked on both.) He was persuaded to join the Defence Research Policy Committee. As a committee-member in the conventional sense, he was practically a non-starter, for the simple reason that he rarely said anything; but that didn't mean he was not cogitating, participating and resolving on action. His action took place outside the committee-room, in private meetings with the members and other people one at a time. "I flit from office to office", he wrote in amusingly candid self-observation — and with a spark of literary talent.

In his days at the Cavendish Laboratory in Cambridge, Cockcroft's colleagues had remarked on his extraordinary gift for switching his full concentrated attention from one objective to another, usually with desired, tangible results in each. This gift served henceforward in affairs, national and international. He flitted from office to office, in London, Washington and Moscow; helping to render balances unupsettable while determinedly edging them in the direction of reason and sanity. It was in his earlier concern with promoting the flow of knowledge, about developments in atomic science, between his own country and the United States that, despite the American preoccupation with secrecy, he began to win the confidence of Washington: through the revival of his old friendship with Rutherford's Russian protégé, Kapitza, he began, against the tide of Russian suspicion, to win the confidence of Moscow. Needless to say he did not get all he wanted, but what he did get was important to all three countries, because it sprang from a deep feeling for human beings and human society in general, for the community of nations. Having been one of the main instigators in establishing in his own country the peaceful use of atomic energy for generating power, he began to speak out for control of nuclear arsenals, playing a part in bringing about the Test Ban Treaty. His political — and moral — stance is splendidly defined at the conclusion of Oliphant's tribute to him:

In politics he was an old-fashioned liberal, seeking always the middle way of decency and fairness. If he was intolerant in any way, it was of inhumanity, the greed and self-seeking of both the extreme right and the extreme left. He never sought power, but when it came to him, he exercised it with wisdom and restraint. □

William Cooper is the pseudonym of the novelist Harry Hoff; his most recent book is Scenes from Later Life (Macmillan, London, 1983). From 1958 to 1972 he was personnel consultant to the United Kingdom Atomic Energy Authority and the Central Electricity Generating Board.

A feeling for the unfathomable

Martin Gardner

Reality and Empathy: Physics, Mind and Science in the 21st Century.

By Alex Comfort.

State University of New York Press:

1984. Pp.272. Hbk \$39.50; pbk \$12.95.

DR ALEX Comfort, trained in classics at Cambridge University, is the British gerontologist who made a fortune with his best-sellers *The Joy of Sex* and *More Joy of Sex*. Discussions with bright students at the Neuropsychiatric Institute, University of California at Los Angeles, where Comfort now teaches, impelled him to set down on paper the ideas that have swirled in his brain since he discovered the joy of QM (quantum mechanics).

Comfort's main theme, like that of many another recent book, is that QM is such a revolutionary new way of looking at the Universe that if it could be "popularly empathized, it would be a blockbuster" (p.25). By "empathize" Comfort means made so intuitively clear that non-physicists could *feel* what it is all about.

The book's first sentence, "Worlds are created by brains", is intentionally ambiguous. You quickly learn that "world" means a world-model, or map, of reality, but later on you encounter the view that perhaps brains have created the outside world as well. Objective reality and mind could be related by what Douglas Hofstadter calls a "strange loop". Somehow — just how is the ultimate mystery — Being was able to bifurcate into matter and minds that allow the matter to see itself. Matter and mind may be epiphenomena of one another, like Escher's picture of two hands, each sketching the other.

Comfort professes to be immune to the epidemic of "pseudo-east nonsense" now infecting the West — what he calls a mix of "Aquarians, acid-heads, and amateur mystics", speaking "yoga-babble" and tossing up "premature Taoists who write popular books on physics" (pp.37-38). The public would do well to stop listening to "itinerant swamis who preach in mottos out of fortune cookies" (p.33), and turn instead to the original sacred literature of Buddhism and Hinduism where they would find that introspection had indeed produced visions in surprising harmony with the empirical results of modern physics.

What do QM and Eastern thought have in common? Comfort believes it is a way of seeing our pluralistic phenomenal world as an illusion produced by an impenetrable, timeless, unfathomable reality. Comfort seldom calls this reality God, preferring instead the impersonal Brahman of Hinduism. Although QM makes no onto-

logical statements, it is nevertheless saturated with anomalies that Comfort thinks support this Eastern insight.

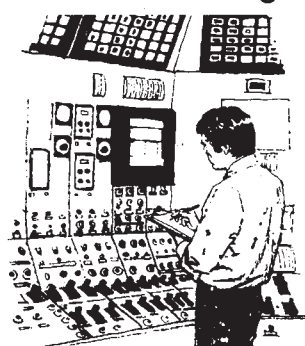
Consider the notorious EPR (Einstein-Podolsky-Rosen) paradox, invented by Einstein and two associates as a thought experiment, but which recently has received strong support from laboratory experiments. Two photons (in one version) are emitted in opposite directions by an interaction that gives them opposing spins. In QM, neither particle has a definite spin until measured, yet the two are so correlated that if you measure *A*, thereby creating, say, a plus spin, *B* will acquire a minus spin even though it may be light years away. It is worse than that. If *A* is measured a second time, it again will acquire plus or minus spin with equal probability. If the spin alters, the companion particle instantly changes to the opposite spin. It is like tossing someone a glove, Comfort writes, then if you turn the companion glove inside out, the other glove will at once invert to preserve the pair's opposite handedness.

Einstein believed that his paradox proved the incompleteness of QM. Comfort agrees. The best way out, he thinks, is to adopt what he calls the "thingless universe" of David Bohm, a QM expert who has long been an admirer of Eastern philosophy. In Bohm's vision, particles are "explicates" of an "implicate order", a substrate that is outside our space and time. Comfort likens the particles to

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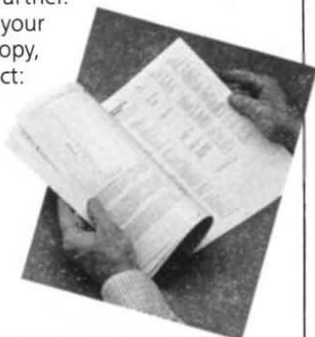
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spots that seem to move on the screen of a computer game. But nothing is really moving. Points of light are merely switching on and off in obedience to signals from invisible hardware. Perhaps Zeno was right. Motion is unreal. The outside world is what the Hindus call *maya*, an illusion conjured up by the motionless Brahman.

It is easy to see how this vision could furnish support for the psi forces that parapsychologists claim are indifferent to space and time. Comfort makes a great potter about his neutrality with respect to psi: "I have no idea whether paranormal phenomena exist or not" (p.229). However, he is a vigorous advocate of what he calls "demonic" conjectures — efforts to see the world in "non-human" ways. It may be, he writes, that altered states of consciousness give authentic glimpses into bizarre but fruitful world-models. He shares with psychoanalyst Jan Ehrenwald, an ardent advocate of psi, the conviction that anecdotal evidence for psi, such as telepathic dreams, is far stronger than any laboratory result. Such evidence is so voluminous, Comfort says, that to attribute all of it to self-deception, coincidence or fraud seems to him like doubting the existence of badgers.

Scientists such as Oliver Lodge, who became Spiritualists, Comfort considers much less credulous than sceptics suppose. They "probably" did not see discarnate spirits, he allows, though they "apparently" did observe "uncanonical transfer of information" (p.218). These are curious remarks to come from a man who insists that his personal estimate of the odds for psi being genuine are fifty-fifty.

Comfort's fondness for demonic models prompts him to look benignly on many other conjectures that most scientists consider hogwash. Rupert Sheldrake, for instance, is persuaded that members of a species are united by a "morphogenetic field". If you train some rats to find their way through a maze at Harvard University, rats of the same species will learn to run the maze faster in Scotland. Sheldrake may be wrong, Comfort admits, but he is raising an important question. Comfort is pleased that Sheldrake's challenge has not affected

colleagues like an "inopportune flatulence in an elevator".

Karl Pribram's holographic model of the brain is another demonic theory that Comfort finds comforting. The Universe may be a monstrous hologram, each tiny part, like one of Leibniz's monads, containing the whole. The book is not yet closed, Comfort is also convinced, on the role of Lamarckism in evolution. His wildest speculation is that sabre-toothed tigers, which flourished before humanity was on the scene, may not have really been "there" except in a vague way, their pale reality sustained only by the low-order brains of the beasts that saw them!

Comfort borrows from Hofstadter the whimsy of interrupting his prose with comic dialogues. A lion and a unicorn step down from a coat of arms to argue about scientific method. A snake named Wilberforce, after the cleric who debated with T.H. Huxley, discusses evolution with a mockingbird. Gezumpstein, a demon from beyond spacetime — his sole task is to invent testable hypotheses — models reincarnation with a row of isolated spots created by painting a line along one side of a helix. Adam demands of God, his psychiatrist, that she reveal the real reason why he was kicked out of Eden.

The cleverest of these interludes tells how Gezumpstein's conjectures take the form of balloons. He distributes them to scientists who blow them up and keep them inflated until they are punctured by a fact. The facts are called "poppers", a play on the name of Karl Popper. Balloons given to mathematicians last the longest, but no balloon is "popper-proof". Many last for centuries before bursting. Some are allowed to deflate, only later to be blown up again.

The book is stimulating, funny, quirky; marred by a rambling, repetitious, disjointed organization. Comfort has a fondness for awkward terms such as "homuncularity," "pre-scientoid" and "dogsbody", a neologism borrowed from James Joyce's *Ulysses*. He seems to have no interest in any modern Western philosopher except Popper. George Berkeley, who more than any other thinker struggled with all of Comfort's ontological puzzles, is not in the index, though I discovered a trivial reference to him on page 197.

Readers unacquainted with modern physics will find most of the book unintelligible. A section on how each moment of history can be undetermined, even though Brahman is timeless and unchanging — it just is — I found totally opaque. And although I learned much, I finished the book with a dizziness from its endless zigzags, and a feeling that Comfort could have made his points much clearer if he had tried. □

Martin Gardner is a science writer. Among other books he is author of The Whys of a Philosophical Scrivener (Harvester, 1983) and Order and Surprise (Prometheus, 1983).

New in paperback

● *Causality and Chance in Modern Physics* by David Bohm, with a new preface by the author. Publisher is Routledge & Kegan Paul, price is £3.95. The book was first published in 1957 and reviewed in *Nature* 181, 658; 1958.

● *Quantum Fields in Curved Space* by N. D. Birrell and P. C. W. Davies, published by Cambridge University Press. Price is £13.75, \$27.95. For review see *Nature* 297, 166; 1982.

● *Lead Pollution: Causes and Control* by R. M. Harrison and D. P. H. Laxen, published by Chapman & Hall in the *Science Paperbacks* series. Price is £7.95, \$23.

● *The Ecology of Algae* by F. E. Round, published by Cambridge University Press. Price is £22.50, \$39.50. For review see *Nature* 297, 521; 1982.

Marking time

Beresford Hutchinson

Revolution in Time: Clocks and the Making of the Modern World.

By David S. Landes.

Harvard University Press: 1984. Pp.482.
\$20, £17.

AN antiquarian book dealer, speaking of his life's passion which was not only his hobby but also his source of income, once said that book-collecting constituted a disease for which there is no known cure. Professor Landes would admit that lovers of old timepieces suffer from a similar affliction and that the horological version of the disease has long had him in its grip. Fortunately for historians and horologists, the general course of the illness and the patient's symptoms in his case have developed upon somewhat unusual lines. They have caused him to write a book — a book, moreover, which demonstrates not only his enthusiasm for mechanisms but, more especially, his fascination in the civil, scientific and economic reasons which engendered the invention of the mechanical clock, influenced its evolution, and gave rise to the variety of regions in which it was developed.

The period spanned in this book is roughly nine hundred years, beginning with Su Sung's Chinese water-clock, completed by AD 1094, and ending with the advent of the quartz-controlled timekeepers which have effectively brought the story of mechanical timepieces to its conclusion. The account embraces all the civilizations and countries which have made a contribution to horology, and describes the aspirations and frustrations of the protagonists in the story, together with the reactions which they generated.

From the formidable compilation of notes on the main text (78 pages worth), it is evident that the author has not merely relied on the standard horological literature. In this, he has followed the excellent example set by one of his mentors, Carlo Cipolla, another economic historian whose *Clocks and Culture: 1300–1700* (Collins, 1967) represents an earlier attempt to deviate from the "How to do it — Who made it — How much is it worth" schools of horological authorship. It is perhaps a pity that Landes, unlike Cipolla, fails to provide a bibliography. Although all the relevant titles occur in the notes at the end of the book, a full reference, once given, is not repeated, and there are occasions when a brief reference

precedes the full one. Fortunately, the comprehensive index usually provides the answer, but this entails a certain amount of to-ing and fro-ing which is vexing to the reader caught up in following the main thread of argument.

A historian with a practical bent, Professor Landes knows how clocks and watches are made and how they work, and a technical appendix offers the reader a clear explanation of the various forms of escapement — that part of a watch or clock which is the beating heart of all mechanical timekeepers. But this is really subordinate to his greater purpose, which is to consider the role of the mechanical clock and its influence on society.

In the first of three main parts, entitled "Finding Time", the author poses the questions, "Why clocks?", "Who needs them?", and concludes that, in mediaeval China, it was the astronomers who were largely to blame. In fourteenth-century Europe, there was an equally strong desire to make self-acting mechanical models of the Universe. Professor Landes is not convinced that these complicated astronomical machines gave rise to more simple clocks in their turn, but is willing to concede that the theory exists before dismissing it. "Keeping Time" and "Making Time", the other sections, respectively develop the themes of technical improvement and increased accuracy, and of methods of manufacture. The human element, whether applying to the makers or to the users, is always considered, with the result that this treatment of a highly technical subject can be understood and appreciated by a non-technical reader.

Another of Professor Landes's purposes is to analyse the reasons for the rise of a horological industry in one country, often at the expense of another's. Why was the English watchmaking trade in such a decline by the end of the nineteenth century? Were the Swiss really caught napping by the burgeoning Japanese electronics industry in the early 1970s? Was the late nineteenth century machine-made American watch ever a serious rival to the high-grade Swiss and English hand-made product? At the risk of spoiling one story by giving away its ending, I shall say that, yes, the Americans had the Swiss running-scared for a brief period, although the Swiss made a brilliant recovery, partly by exporting a series of "look-alike" watches which had the American public fooled, but mostly by emulating American production methods.

Professor Landes is a humorous author as well as a questioning, impartial one. If he lapses into the occasional colloquialism, it adds to the enjoyment of his book rather than detracts from it. The section headings — "The Man Who Stayed to Dinner" (answer, John Harrison) and "Who Killed Cock Robin" (pass) — are examples of well-chosen titles which refer to section contents. His impartiality stems from wide reading and a total grasp of his subject, though this is to accuse him neither of sitting on the fence, nor of producing a "scissors-and-paste" book.

Are there any gaps in the presentation? Landes might have laid more stress on the fact that the precision timekeepers used at sea and in observatories led to a general raising of standards in domestic clockwork, especially in the late eighteenth century. More recently, what about the electric

synchronous clock, which was heralded as bringing accurate time from the national grids into everybody's home from the 1930s onwards? No mention of those, as far as I can see, and never mind at that: I would not have one in the house, any more than I should care to wear one of the electronic miracles on my wrist.

It is obvious that even horologists' passions can be aroused, and there are doubtless some passages in Professor Landes's book which will provoke discussion in other circles. In the meantime (no pun intended, as Landes says in his account of Greenwich), read his book and, preferably, purchase your own copy. Failing that, look out for it in the reference library under the general series 681, and keep on pestering your librarian until it appears. □

Beresford Hutchinson is Curator of Horology at the Old Royal Observatory (National Maritime Museum), Greenwich, London.

Art of the clock-maker — a French striking clock in the form of a suspended terrestrial globe, by Jacques de la Garde, Blois, 1552. Originally it would have been fixed in the centre of an armillary sphere.

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Wizard of domes

David E.H. Jones

Inventions: The Patented Works of R. Buckminster Fuller.

By R. Buckminster Fuller.

St Martin's Press: 1983. Pp.316.

1.75 kg, \$40.

THE most dramatic spiritual conversion leaves the same person underneath. R. Buckminster Fuller, whose 28 patents are collected in this heavy tome, is a case in point. In 1927, at the age of 32, seeing himself as a total failure and contemplating suicide, he made instead a profound resolution to commit "ego-cide". Abandoning concern for himself, he dedicated his life to the problems of all humanity, to find out what one man could do to solve them. As the subject of this personal experiment, he nicknamed himself "Guinea Pig B" (B for Buckminster). What shines through this work is that Guinea Pig B was an outrageous egotist.

Fuller is an appalling writer. He is capable of explaining his commitment to a "never-again-for-self-use employment of my omni-experience-gained knowledge". And since this book consists of his patent applications — a forbidding literary form even in skilled hands — and his adulatory comments upon them, reading it is like trying to bicycle through sand. Further-

more, Fuller's ideas are very variable. Some of his inventions, such as his "Dymaxion car" of 1933, now seem very shallow exercises; and his thinking is often woolly. Thus he repeatedly claims that some of his structures are far stronger than stress-analysis would predict, and that a mysterious "synergy", unpredicted by the properties of their components, is at work within them. He is also given to sloppy philosophy and sixties-style eco-nut moralizing. This aspect of his thinking cannot command respect.

But Fuller was also one of the great originals of American engineering. He could imagine in three dimensions, and his most interesting patents are those concerned with three-dimensional structures: 11 geodesic domes, one space-filling girder lattice, and a world map. They were devised between 1944 and 1975; his major contribution to engineering only began to crystallize 30 years after he began his career as Guinea Pig B. Geodesic construction was not new when he came to it (Barnes Wallis had used it in the Wellington bomber). But his development of it into a practical architecture for big domes shows real engineering genius. And tensegrity construction is Fuller's alone, and it is wonderful. It produces a rigid stressed lattice with no continuous compression frame; Patent 15, which introduces this seemingly impossible form of construction, is to my mind the most compelling in the book. It is worth persevering with the convoluted description to gain an understanding of how such an audacious structure can work. The idea is a splendid vindication of Fuller's resolve of 1927: it exemplifies perfectly what one independent and original mind can contribute to the world.

And yet for engineers, tensegrity construction is still just a clever idea. Even the geodesic dome remains a specialized and rather self-conscious architectural form. And none of Fuller's other inventions has been seriously taken up, or has contributed to the idiom of modern engineering. Not much of Fuller's thinking has changed the world we live in; in a sense, his most important invention was himself. For over half a century, Guinea Pig B pursued his individual path of engineering creativity quite outside the American scientific and technological establishment. But this his last book, beginning with his relentlessly congratulatory introduction and ending with his 43 honorary degrees (each with its fulsome dedication) compels the thought that, so far at least, the main global effect of his bold and courageous career of self-effacement has been to gain renown for its author. □

David E.H. Jones is a guest staff member of the Physical Chemistry Department, University of Newcastle upon Tyne, and a science consultant to industry and the media. He is author of The Inventions of Daedalus: A Compendium of Plausible Schemes, published by W. H. Freeman in 1982.

Waves, particles and paradoxes

John Stachel

The Tiger and the Shark: Empirical Roots of Wave-Particle Dualism.

By Bruce R. Wheaton.

Cambridge University Press: 1983.

Pp.355. £22.50, \$39.50.

X-RAYS have become a household word through their medical uses. Yet their discovery by Wilhelm Röntgen at the end of 1895 launched a tremendous publicity wave for the phenomenon, a then exotic and glamorous topic. Röntgen must have been one of the earliest physicists to pen the now familiar complaints: "I could not recognize my own work in the reports any more . . . Gradually I became accustomed to the uproar, but the storm cost time. For exactly four weeks I have been unable to do a single experiment!". The glamour gradually wore off, but puzzlement as to the nature of the new radiation did not.

The object of Bruce Wheaton's book is

. . . to clarify the developing understanding of X-rays and related phenomena early in the twentieth century. But it is the physicists' growing awareness that [classical] electromechanical explanations of the radiation would not work in principle that forms the real subject of this book [p.2].

The method by which he seeks to realize this goal is a detailed reconstruction of the course of experimental and theoretical studies of X- and γ -rays, and some related topics in optics and atomic structure, from the discovery of X-rays until the presentation of de Broglie's thesis in 1924, summarizing his work on the wave-particle duality for ordinary matter. One of the most striking features of the book is the meticulous care with which experimental investigations and the theoretical controversies which they stimulated are reconstructed. The rigour with which Wheaton strives to avoid introduction of anachronistic elements into his discussion (he apologizes profusely at one point when he feels such an omission would be too confusing), helps to convey to the reader a real feeling for the "state of the art" at various periods, including the confusions and wrong turns, as well as a sense of the undoubted if irregular long-run progress made in the understanding of these new and puzzling phenomena. Here we are far indeed from sanitized text-book versions of the history of great scientific discoveries. This feature of the book should make it of interest to many readers with a general interest in the history of science, over and above its obvious appeal to specialists in the history of quantum theory.

Wheaton details the early controversies over whether X-rays were particulate or electromagnetic in nature; and, if electro-

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magnetic waves, whether transverse or longitudinal, pulse-like or periodic. He stresses the key role that the pulse interpretation played in the transition between classical and quantum viewpoints. Once the wave view predominated, studies of the ionizing properties of the new radiation confronted physicists with what Wheaton calls the paradoxes of quantity and quality: how could any wave-like disturbance, whose energy spreads out spherically from a central target, ionize only a few of the atoms in the surrounding region; and how could secondary electrons so produced each have about as much energy as the primary electrons whose deceleration at the target produced the rays in the first place?

Physicists here faced the fundamental paradox which was to remain unresolved for two decades: a wave-like disturbance manifested properties most readily explained by the assumption that the disturbance consisted of particles! Attempts to dodge this paradox are considered by Wheaton, notably the triggering hypothesis (X-rays only trigger the release of energy stored within the atom) and Bragg's attempt to suppress the wave aspect of the paradox by asserting that X-rays were nothing but a particle beam. Such attempts were definitively ruled out by the discovery in 1912 of X-ray diffraction by crystals.

Similarly paradoxical features of visible light had been elucidated since 1905 by Einstein who, by 1909, was publicly calling for a theory of light which somehow united wave and corpuscular aspects. Wheaton suggests that "our story developed quite independently" of Einstein's "imaginative and prescient statistical treatment of light" (p.xvii). But recently discovered letters from Einstein to Sommerfeld (*Physikalische Blätter* 40, 29; 1984) show that Einstein was involved in the discussion, during 1909 and 1910, between Stark and Sommerfeld over the interpretation of the observed angular asymmetry in X-ray intensity. Einstein stressed the paradoxical features, insisting (at a time when this was not clear to everyone) that light and X-rays differ "only qualitatively".

The little Wheaton has to say about Einstein's role in the quantum story includes one major inaccuracy. He insists that Einstein's special theory of relativity was "diametrically opposed to the aether ontology", and succeeded in "eliminating the aether altogether" (p.106). Einstein was at pains to stress (in one of the aforementioned letters to Sommerfeld, among other places) that relativity theory required no stand on such ontological issues. It forced relinquishment of a *mechanically* interpreted aether, but was quite compatible with a non-mechanical aether. Indeed, Einstein's earliest attempt to resolve the wave-particle paradox was a unified theory (of electrons and light quanta) based on such a non-mechanical aether field.

X-ray diffraction work, together with the inhibiting effects on research of the

First World War, put a temporary stop to most experimental studies of the particulate aspects of radiation (with the notable exception of Millikan's work on the photoelectric effect). The great successes of the Bohr theory from 1913 on in understanding atomic structure and identifying atomic energy levels posed most acutely the question of the photoelectric effect and its X-ray and γ -ray analogues. Post-war work on these problems made it more and more difficult to avoid facing up to the wave-particle paradoxes, first glimpsed over a decade earlier. Maurice de Broglie's group in Paris, which included his younger brother Louis, played a prominent role in this research. Wheaton shows how this work formed a natural background out of which Louis's brilliant idea of transferring the wave-particle paradox from radiation to matter could emerge. With a brief indication of the stimulating effect of de Broglie's work on the ideas of Einstein and Schrödinger and the experiments of Davisson and Germer the book ends. Readers may want to consult Vol.1 of Mehra and Rechenberg's recent *Historical Development of Quantum Theory* (Springer-Verlag, 1983) for additional details on and somewhat different interpretations of de Broglie's work and various other topics treated by Wheaton.

Wheaton tries to weave into the book a running contrast between "the mechanistic bias of British physicists" leading to the "British proclivity to seek mechanical models" (pp.5-6) and "German mathematical physicists" who "were not deterred by an inability to represent physical concepts mechanically" (p.7). He himself notes that "Larmor in Britain held views similar to those of many Germans" (p.7) and we can at once add the names of Poynting, Campbell, Pearson and Eddington to the list of British crusaders against mechanism. On the other hand, prominent German theoretical physicists such as Voigt, Boltzmann and Helmholtz (and the adolescent Einstein in his first scientific essay!) expended considerable effort to construct mechanical models of the electromagnetic aether. Given that we are talking about a small number of physicists in each country, it is hard to see which names go to make up the rule and which constitute the exceptions. It would seem wiser at this time to try to trace out the growth and interrelationship of smaller units, such as schools centred around leading figures or centres of physics research, rather than attempt to make sweeping generalizations about national styles of scientific research. For example, how would Wheaton explain the fact that "Deutsche Physik", of which Lenard and Stark were to boast a decade after Wheaton's story ends, prided itself on just those characteristics he attributes to British proclivities? □

John Stachel is Professor of Physics at Boston University, and Editor of the collected papers of Albert Einstein, the first volume of which is scheduled to appear next year.

Putting the heavens to order

Owen Gingerich

Ptolemy's Almagest.

Translated and annotated

by G.J. Toomer.

Duckworth, London/Springer-Verlag, New York: 1984. Pp.693. £55, \$64.

CLAUDIUS Ptolemy's geocentric system has long since been dumped into the dustbin of discarded theories. Why, then, is anyone still concerned with his hoary treatise? It is because Ptolemy's *Almagest*, more than any other book, convinced people that the seemingly complex phenomena of the heavens could be represented by a simple

IMAGE
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Star gazer — Ptolemy depicted on the Campanile del Duomo, Florence.

underlying mathematical description, one that afforded the possibility of continuing prediction of celestial events. Certainly this was a milestone in the development of science.

G.J. Toomer's new English edition of Ptolemy's classic treatise is more than just a fresh translation. It is a most intelligently arranged presentation with a running, critical commentary at the foot of nearly every page, and it is based on a new reading of both the Greek and Arabic manuscripts. Included are a score of supplementary diagrams that clarify (especially) Ptolemy's instruments and his complex latitude theory, a brief introductory section that clues in the reader with respect to the technical background that Ptolemy assumes (such as ancient calendrical systems), and three appendices that give examples of numerical problems and textual variants. What Toomer has produced is the best edition in any language, one that will remain the standard preferred text for years to come. *Ptolemy's Almagest* is clearly the most important volume for the history of ancient science since O.

Neugebauer's *A History of Ancient Mathematical Astronomy*, published nine years ago by Springer-Verlag.

In many respects, Ptolemy's work is to applied mathematics as Euclid's *Elements* is to pure mathematics. The *Almagest* begins with instructions for computing the trigonometric chord function, and continues by applying these in a long series of proofs, constructions and specific derivations of numerical parameters from his observational material. Fortunately Toomer has not hesitated to use an anachronism, the equals sign (which did not come into common usage until the sixteenth century), and he has carefully arranged his equations with the equality at a fixed position in the middle of the page. He has also adopted a double degree sign, $^{\circ}$, for the "demi-degrees" that Ptolemy uses in order to facilitate his clumsy trigonometric manipulations. This attention to detail has produced a new level of elegance for the work, and, in combination with highly specific running heads, makes Ptolemy accessible as never before.

Ptolemy's attempt to be the Euclid of applied mathematics was fraught with certain difficulties, because observational data are not quite as tidy as the abstractions of pure points, lines and spaces. It is thus not surprising that his pioneering effort harbours certain ambiguities and outright botches. Untamed nature is not so easily brought into a mathematical harness. In his preface, Toomer allows that Ptolemy has manipulated his material "in order to present an appearance of rigor in his theoretical treatment which he could never have found in his actual experience". Indeed, Ptolemy, like astronomers today, undoubtedly built his edifice on a great array of traditional techniques and data, rejecting, adjusting or incorporating them as he saw fit. To examine how these various elements blend together is both a fascinating and a worthwhile research endeavour.

Not everyone has been willing to investigate Ptolemy with such scholarly calmness. In his *The Crime of Claudius Ptolemy*, published in 1977, the Johns Hopkins geophysicist R.R. Newton maintains that Ptolemy's work is riddled with deceit and concludes that it would have been better for astronomy if the *Almagest* had never been written. Newton's conclusion is at worst so extreme as to be silly, and at best a debating point. The problems of the *Almagest* deserve critical and informed discussion, Toomer writes, but he adds that Newton's book "provides nothing of the kind, but rather tends to bring the whole topic into disrepute". Although Toomer chooses not to debate with Newton in the present forum (wisely, in my opinion), he scores numerous points in his careful examination of the text. Here are two examples.

● Ptolemy's tables for the mean motions of the planets do not come up to his own epoch except by an extra addition,

thereby bringing forth the charge in some quarters that these tables were pilfered from an earlier source. "Despite Ptolemy's clear statement here of his motivation [for the arrangement], it has been the subject of much fruitless debate", notes Toomer on p.140. "By the time he came to compose the Handy Tables, he had realized the inconvenience of this arrangement, and switched. . .".

● For some centuries there has been speculation that Ptolemy's extensive star catalogue, which occupies the better part of two of the 13 books comprising the *Almagest*, was taken over wholesale from his predecessor Hipparchus. There exists no direct evidence, however, for any systematic set of numerical positions compiled by the earlier astronomer. While Toomer does not argue for Ptolemy's originality in compiling the catalogue, he makes it clear that he believes any attempt to credit the positions to Hipparchus is unfounded. In commenting on the text

leading up to the actual star list, he notes (p.330) that

all the evidence is in favour of the hypothesis that Hipparchus did not record stellar positions in latitude and longitude (except for a few special cases. . .). Otherwise it is impossible to explain why Ptolemy went through the cumbersome process of comparing declinations, instead of simply comparing latitudes observed by Hipparchus and himself.

Extensive though his notes are, Toomer does not speculate on the origins of the Ptolemaic planetary models, nor on their development in Ptolemy's later works. Nevertheless, this monumental volume now paves the way for further investigations of what, precisely, was going on in ancient applied mathematics, an analysis that should bring a fuller understanding of the roots of our own modern science. □

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Picture astronomy

Stephen P. Maran

The New Astronomy.

By Nigel Henbest and Michael Marten.

Cambridge University Press: 1983.

Pp.240. £12.50, \$24.95.

IN *The New Astronomy*, Nigel Henbest and Michael Marten celebrate the recent achievements made through digital image processing and (for some spectral regions) through the use of two-dimensional detectors. In computer-generated astrophysical images, colour may represent intensity or polarization of light, a physical parameter such as temperature or strength of magnetic field, or the rate of change of any such quantity with position in the sky. So not only are the pictures reproduced in this book of aesthetic appeal, they are pregnant with information.

Some of the most dramatic contrasts between separate views of the same object are provided by jovian imagery. Compared with a highly-detailed *Voyager* photograph of Jupiter, infrared scans show a seemingly more ordered planet, while radio and X-ray images are so different from the usual picture that an uninitiated astronomer might well mistake the target. The X-ray Jupiter comprises two separate sources, but 6-cm radio waves define a tripartite Jupiter, a central oval flanked by two smaller patches, orientated at right angles to the X-ray sources. Especially striking are correlated sequences depicting emission from the jovian magnetosphere: the pattern of 21-cm wavelength continuum sources wobbles up and down as Jupiter spins, while in the corresponding radio polarization maps the dominant mode of circular polarization reverses as the planet presents first one magnetic pole towards

the Earth and then the other.

The educational impact of the illustrations in *The New Astronomy* is typified by the colour-coded radial velocity maps of the Andromeda galaxy. From these it is clear which side of the galaxy is turning away from us and which side towards us; shades of red (as in redshift) denote recession velocities and approach velocities are represented by cooler green and blue, while off-colour patches signal velocity pattern disturbances that may correspond to density waves which maintain the spiral arms.

A few points, if addressed, should lead to an even better second edition of the book. The presentation of visible, ultraviolet and X-ray solar images would be much improved if these were based on photographs made on the same date and thus referring to the Sun in the same condition. Consistency has gone too far in the captions for a set of ultraviolet, X-ray and gamma-ray sky maps. In each, the wavelength is expressed in nanometers, but this, together with deliberate avoidance of powers-of-ten notation, results in a description for one map (" $0.000\,000\,2 - 0.000\,02\,\text{nm}$ ") that neither novice nor expert can appreciate. Finally, some images need marker lines at the borders, or some judiciously applied arrows: few readers will identify Eta Carinae in the photograph of complex nebulosity from the information that the star is "at the lower-left end of the small banana-shaped dark cloud".

For the non-specialist, this is a fine guide to the spectacle of modern astrophysics. Professional astronomers will find the book, with its detailed list of picture sources, the right place to identify the best new illustrations for lectures and articles. □

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Variable stars

Nigel Calder

The Solar System.

By Roman Smoluchowski. Pp.174.

The Discovery of Subatomic Particles.

By Steven Weinberg. Pp.206.

Fossils and the History of Life.

By George Gaylord Simpson. Pp.239.

Human Diversity.

By Richard C. Lewontin. Pp.179.

The Science of Musical Sound.

By John R. Pierce. Pp.242.

Volumes in the Scientific American

Library, published by W.H. Freeman.*

Each book £10.95.

SERIES of books are to be mistrusted because the initial concept can all too easily become a substitute for later thought. I paused when I saw the titles of this batch of five from the Scientific American Library. After the unlikely *Powers of Ten*, the first under this new imprint (reviewed in *Nature* 306, 125; 1983), they seemed too obviously the topics that anyone might jot down on the back of an envelope when proposing a series of popular books on science: planets, atoms, fossils, human genetics — oh, and music to prove you are not philistine. The difference here comes in the quality of the authors, who combine eminence in their fields with proven gifts of exposition.

In the flotilla leader, *Powers of Ten*, Philip and Phylis Morrison in collaboration with Ray Eames brought full circle the idea of depicting the world at different scales, from the intergalactic to the subatomic. That concept originated in Kees Boeke's book *Cosmic View*, was developed in two movies by Charles Eames, and came back between covers in the new and more vivid book. With the handsome volumes in front of us, and others from such authors as Christian de Duve, James D. Watson and David Hubel coming over the horizon, all of them propelled by the enthusiasm of Gerard Piel of *Scientific American*, what response can there be but immediate surrender to this firepower?

Doubts persist because these beautifully

*In the United States these books are first made available only to members enrolled with the Library (for details write to W. H. Freeman, 41 Madison Avenue, New York, NY 10010). In general, titles are then released to the book trade about one year after their initial appearance. Currently available through the trade are *Powers of Ten* (\$29.95), and *Human Diversity* and *The Discovery of Subatomic Particles* (\$27.95 each). The other titles reviewed here will be released later this year.

In the United Kingdom, Europe, Africa and the Middle East all the above titles are available through the book trade in the usual way. New titles can be obtained through the trade as they are published, at approximately two monthly intervals. *On Size and Life* by Thomas A. McMahon and John Tyler Bonner and *Perception* by Irvin Rock will be available in May, both at £14.50.

printed and illustrated books look very similar. That raises another problem about series: either the authors are forced unhappily into a procrustean bed of editorial devising, or else their idiosyncracies pop out unconformably, which may be confusing to readers who expect one kind of book and get another. Although I am glad that the Scientific American Library (they do not call it a series) veers towards individuality rather than predictability, the standard format carries an implication that the reader who can cope with the fossils should also be happy with the physics. For these reasons, the books must be judged individually, yet also as a variety of solutions to the problem of presenting expert knowledge to a general readership.

The most straightforward exposition is Roman Smoluchowski's *The Solar System*. This is the space-age Solar System, with all the new imagery to draw on (including a composite *Voyager* view of the south pole of Jupiter with a giant Jovian crustacean in the middle, which turns out to be "an artifact of the imaging process"). We also have Venus mapped by radar, and astronauts on the Moon. The book summarizes the latest knowledge about each object in turn, and comments on current riddles — the missing solar neutrinos, Mercury's magnetic field, Venus's retrograde motion, the evidence for the past torrents of water on Mars, and the "astounding" revelations about Saturn's rings. The essay on Jupiter, Saturn and their respective moons is the best in the book, and makes an interesting contrast with the earthbound speculations about Uranus and Neptune; *Voyager 2* will not reach Uranus until 1986. Smoluchowski's afterword on life in the Sun's environment leads to a robust though "disappointing" conclusion that "it is most unlikely that any form of even the most primitive life exists now in the solar system outside the Earth".

Entirely different in approach is Steven Weinberg's *The Discovery of Subatomic Particles*. From a recent Nobel prize-winner, readers might well expect a stop-press report on charmed quarks, W particles and the like. If so, they will be disappointed: this is prehistory, centred on events at the Cavendish Laboratory between 1897 and 1932, with only a brief postscript about mesons, strange particles and quarks. While Weinberg indulges his evident pleasure in the story, he uses "flashbacks" to explain the classical physics underpinning the subatomic discoveries. For example he starts off with J.J. Thomson identifying the electron, but immediately interrupts himself with 15 pages of historical disquisition on electricity, discharges in vacuum and Newton's laws of motion, while poor J.J. is waiting to switch on his apparatus. I do not believe this is how non-physicists want to hear about it. Weinberg's crypto-mathematical approach also makes the progress of physics early in this century seem logical and robot-like, rather than the roller

coaster that it really was, and we are denied the intellectual climax to the story because the quantum theory falls outside his self-imposed syllabus.

A book from George Gaylord Simpson, the guru of American palaeontology, is all the more welcome because he defied illness to complete *Fossils and the History of Life*, which is packed with authoritative information. It is also conservative in its treatment of current controversies in palaeontology. Even continental drift comes as a postscript to the traditional biogeography of waif dispersal and land bridges. The Eldredge-Gould critique of phyletic



Illustration Library-style — the picture, of Robert Wadlow who was 8 feet 10¾ inches tall at the age of 20, is reproduced from *On Size and Life*. See the footnote on this page for publication details.

gradualism is described as an attack on a straw man. Other heresies get shorter shrift: the neutral theory of molecular evolution, the evidence for a cosmic impact terminating the Mesozoic and the banishment of *Ramapithecus* from the human lineage. That may be a pity because if these ideas prevail, as some now seem likely to do, Simpson's dismissal of them may diminish the long-term value of the book. Moreover, when his treatment of evolutionary mechanisms becomes argumentative, the author's use of language slips from vivid explanation into the denser terminology of the seminar.

Like Smoluchowski's *The Solar System*, Richard Lewontin's *Human Diversity* is a wonderfully updated exposition of an old theme. Yet for every hundred people who have seen spectacular spacecraft images of the planets, I doubt if one is familiar with the discovery by Lewontin and Harry Harris of the wholesale molecular polymorphisms. They illuminate the genetic similarities and differences between indivi-

duals and between populations, and also reflect the migrations of identifiable human groups that kept acquiring differences and then re-stirring the genetic pot. The biochemistry does not entail genetic determinism. Lewontin stresses the plasticity of the human endowment, and the interaction of genotype and environment in producing adult variations. "The heritability of MN blood type is 100%, and the heritability of the ability to pronounce *rue* like a Frenchman is zero". *Human Diversity* is a book that non-biologists will have to read carefully, because of a spattering of jargon and the subtleties of the subject, but the effort will be well rewarded.

While Lewontin's takes pride of place on my shelf as arguably the most important book of the five, it is Pierce's that finishes up at my bedside — also on my record player, because two disks come with *The Science of Musical Sound*. This is a personal and practical exploration of the subject by a distinguished electronics engineer who, besides being a pioneer of computer-generated music, also writes science fiction as J.J. Coupling. From a deceptively elementary start with the behaviour of stretched strings, the reader soon finds himself among the paradoxes and illusions that flower in the no man's land between physics, perception and art. Whether Pierce is dealing with scales, harmony, loudness or timbre, or with misadventures in architectural acoustics, he combines a lucid and lively presentation of the facts with shrewd discussion of the mysteries. His message is that the computer transcends all the limitations of previous musical instruments and offers many novel effects; these await only the supply of new genius that is not overpowered by the genius of the past. Although *The Science of Musical Sound* is entirely different in content and style from *Powers of Ten*, which I mentioned at the outset, they share an enthusiasm and delight which are muted in the other books.

From this batch of books, what should we conclude about the merits and problems of series-like publication of science for a general readership? The authors all have star quality, but inevitably they appear with variable magnitudes in this constellation. My guess is that the best of the books (Smoluchowski, Lewontin and Pierce) would have appeared willy nilly, from authors already full of their ideas. If the Scientific American Library is to take well-deserved credit for giving them a ride in its gleaming vehicle, then equally a question hangs over others that have an air of coming aboard to oblige the driver. These, I must stress, are in the minority. Quality control in the production of popular science, as with all books, is nevertheless a matter of making quite sure that every author has a fresh and exciting story to tell.

Nigel Calder is a science writer. His most recent book is Timescale: An Atlas of the Fourth Dimension (Chatto & Windus, 1984).

Grand organization in mind

Stuart Sutherland

Frames of Mind: The Theory of Multiple Intelligences.

By Howard Gardner.

William Heinemann/Basic Books: 1984.

Pp. 438. £18, \$23.50.

UNTIL about forty years ago, the fashionable psychologist rose to fame by proposing majestic theories that were *une grande mélange de tout*. William James, Ivan Pavlov, J. B. Watson and the Gestalt psychologists took the whole of human behaviour into their purview. The last in this romantic line was Donald Hebb: I remember the excitement generated in 1949 by the publication of his book, *The Organisation of Behaviour* — a typically modest title. Unfortunately, most of the theorizing in such books was as vague as the scope was broad, and psychologists came to work in more restricted domains. They felt it better to provide rigorous explanations for such fascinating phenomena as the movement evinced by a stationary point of light in a dark room or the faster learning of nonsense syllables at the beginning and end of a serial list than of those in the middle. Now, after a gap of 35 years, Howard Gardner has reverted to the grand tradition. No one can challenge the scope of *Frames of Mind*: it remains only to debate its rigour.

Gardner puts forward a faculty psychology. The idea that the human mind contains discrete and autonomous faculties is of course not new. It gave rise to phrenology and was subsequently defended by such practitioners of mental testing as L.L. Thurstone and J.P. Guilford. They attempted to uncover the different faculties by giving subjects an array of tests and performing a factor analysis on the results in order to extract a small number of hypothetical factors that would account for the correlations between the individual tests. As Gardner rightly points out, the enterprise foundered because there is no one solution to a factor analysis and because the tests given were arbitrary.

Gardner's originality lies in the composition of the seven faculties into which he claims human intelligence can be divided, and in proposing seven "unmistakable marks, by which you may know, wheresoever you go, the warranted, genuine" faculty. He describes his faculties as "intelligencies", but I shall keep to the old-fashioned word "faculty" since intelligence is not a count noun and to use it as one is a mockery of Gardner's first faculty, that for language. The other faculties he proposes are musical, logical-mathematical, spatial, bodily-kinaesthetic, and intra- and extrapersonal. Spatial ability is the capacity to manipulate the world in the imagination: it is required for map-

reading, for much of science, and for all painting; bodily-kinaesthetic ability is required both for moving the body and for manipulating the external world and is, according to Gardner, a prerequisite for dancers and inventors. The intrapersonal faculty is used to understand oneself, while the interpersonal one is for understanding others: Gardner seems in some doubt whether to classify these as two separate faculties or as different aspects of the same one.

Some may feel a sneaking suspicion that Gardner chose his seven faculties through common sense and then looked for supporting evidence by the use of his criteria, but that is a perfectly legitimate way to proceed. The criteria he has devised are as follows. First, each faculty should depend on a set of core operations that differ from one faculty to another. Many of the computations needed to use or understand language are clearly different from those needed by the spatial or bodily-kinaesthetic faculties. To understand language, however, it is surely necessary to make use of all the remaining faculties (though which is needed at any instant will depend on the topic of discourse), a point which Gardner does not adequately consider. Second, the existence of a particular faculty may be inferred if there are brain lesions that damage its operation while leaving the others unimpaired: showing that the computations underlying each proposed faculty are carried out in different parts of the brain is presumptive evidence that the computations themselves are different. This criterion works moderately well for most of the faculties, but it seems doubtful if personal intelligence can be impaired by brain damage without deterioration in many of the others.

A third and novel criterion is the existence of a heightened form of a single faculty in *idiots savants*, whose other abilities are severely impaired. They may attempt to compensate for a general loss in intelligence by developing to their utmost any faculty that has been spared. Some *idiots savants* have shown remarkable ability at such tasks as calculating the day of the week on which a particular calendar date falls, though it should be noted that none have become great or even good mathematicians. It is in fact open to question whether rapid calculations and real mathematical ability have much to do with one another.

Among the other criteria that Gardner uses are a distinctive evolutionary and developmental history for a given faculty. Neither of these is very compelling. We know little about the evolutionary history of most of the faculties he identifies, and it may be that in the individual the development of one faculty is tied to progress in another: thus, a child can hardly begin to enumerate objects (logical-mathematical) before having the concept of an object (spatial) and without some spatial knowledge it could not display much in the way of

manipulative (bodily-kinaesthetic) skills.

Gardner further proposes that it should be possible to encode the operation of any faculty in a symbol system. This criterion is in part empty since almost all conscious thought processes can be so encoded. However, one of Gardner's faculties, bodily-kinaesthetic, is very difficult to encode as anyone who has attempted to teach golf to beginners well knows. Moreover, it is extremely difficult to encode unconscious aspects of other faculties, for example, syntax, and Gardner's use of this criterion is obscure.

His final criterion is that there should be more correlation between the results of tests that depend on the same faculty than between those that depend on different ones. This appears to be true of tests of linguistic and spatial skill, and although Gardner does not mention it, it is also true of tests of bodily ability. Less favourable to Gardner's thesis is the fact that whenever a battery of tests is given, the results on all tests tend to correlate with one another (with the possible exception of tests of body skill). It is of course precisely on these correlations that the notion of general intelligence (or *g* as Charles Spearman called it) is founded. Gardner does little or nothing to explain why, if the different faculties are completely independent, there should be such a high correlation between tests that ostensibly draw on several of them.

I have already noted that the development of the faculties may not be independent and that more than one may be used in the same task. The latter point Gardner himself acknowledges, but he fails to draw an important conclusion. In order to integrate the results of computations performed by two or more faculties, there must be some further computational mechanism at work that lies outside the individual faculties. Gardner decries the need for such a "horizontal" mechanism, but does not consider the question carefully enough. In the extreme case, the system could break down because one faculty was waiting on an input from a second in order to do further computation, while the second was waiting for an input from the first. For the same reason, Gardner's treatment of metaphor is weak: how could one faculty take as a metaphor something drawn from another unless it had a knowledge of how the other worked? A further argument that there is a superordinate mechanism to coordinate the knowledge processed in each of the faculties may be drawn from the effects of frontal lobe lesions, which often severely impair the ability to plan: this impairment is not limited to any one of Gardner's seven faculties.

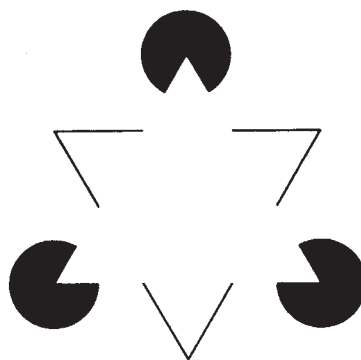
If Gardner is weak on the horizontal organization of the mind, he is even weaker on its vertical organization. By almost all of the criteria he lists, vision and audition should be special faculties though much of their output is fed to other faculties (for

example, audition makes possible both language and music). Again, it is well known that anterograde amnesia can be produced in all domains by damage to the hippocampus. Even if memory is not a horizontal ability, this finding suggests that the different faculties share some common mechanism for the laying down of new memories.

One can also ask whether Gardner has cut his faculty cake correctly. It is in fact not easy to think of tasks whose performance cannot be accounted for by knowledge embedded in his seven faculties, but this is partly because several may be employed in the same task. Nevertheless, one could ask in which faculty resides a wine-taster's skill or even the ability to discriminate sounds that are neither verbal nor musical.

Despite the interest of Gardner's general thesis, his book has several annoying de-

Trick of perception



In this diagram the eye sees contours that are not present (illusory contours), and the figure so defined seems whiter than the surrounding area. The illustration is taken from Irvin Rock's *Perception*, a volume in the Scientific American Library. See footnote on p.791 for publication details.

fects. The worst is a trait that he shares with his predecessors in the grand tradition — vagueness. Nowhere does he try to characterize in rigorous terms the operations carried out by the different faculties. Indeed, he decries computer simulations (which are the only rigorous theories of mental activities yet constructed), largely on the grounds that they are not biological. If he examines the work of David Marr and others, he will find that computer models can take into account neurophysiological findings. There are other passages where he is alarmingly naive: for example, he avers that work demonstrating the existence of cells that respond selectively to complex objects, like a hand or a face, has thrown much light on object recognition. Such research has not in fact illuminated this problem, since to understand how an object is recognized we would need to know how the cell is wired-up. He also has a habit of ducking difficult issues: he writes, for example, "The philosophical ambiguity that surrounds the concept of mental imagery can also be left to the experts".

Gardner is an enthusiast, who, like the Beaver, goes "bounding along on the tip of his tail". He is extremely discursive, a trait that will please anyone wanting a superficial romp through science, music, painting, architecture, dancing, baseball and so on, but that may well dismay anyone interested in rigorous arguments and upset anyone with much knowledge of the topics covered. His surveys too often lead him to such unremarkable conclusions as "One cannot aspire to be a poet without sensitivity to the interaction among linguistic connotations", "painting and sculpture involve an exquisite sensitivity to the visual world as well as an ability to recreate it in fashioning a work of art", or "certain features typically characterize the baseball player . . . there is . . . the ability to throw the ball where one wants it". It is perhaps no accident that in discussing science, Gardner fails to mention that one of its main attributes is the rigour with which its theories are expressed. His book also contains potted accounts of such figures as Von Neumann, Einstein and Rubinstein, and lengthy excursions into anthropology to illustrate how the different faculties are exhibited in different cultures. It ends with a lengthy section in which Gardner attempts to apply his notion of faculties to education. Much the most interesting part is an account of the Suzuki method of musical education developed in Japan. Infants are trained almost from birth, and can often play violin concerti faultlessly by seven years of age. But Gardner's own recommendations are as vague as those of most other educationalists. "Early assessment . . . allows an individual to proceed as rapidly as seems warranted in those intellectual channels where he is talented, even as it affords an opportunity to bolster those intellectual endowments that seem relatively modest".

Gardner is a polymath, who has clearly developed all seven faculties, though as the quotations from his book suggest, his linguistic faculty could, in his own words, do with bolstering. His main thesis is interesting, but it is a pity he did not cut the trimmings, many of which are banal, and concentrate on working it out in more detail. In particular, he might have attempted to characterize more carefully some of the operations conducted in each domain, to give a more detailed and careful account of the horizontal interactions between faculties, and to deal more thoroughly with perception, memory and planning. Too often he prefers to leave the hard work to someone else. One suspects that once we know what are the computations performed by the mind and how the requisite software comes into existence, it will become clear that human faculties are much more blurred than he would have us believe or even that they are as elusive as the Snark itself. □

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Confessions of a biologist

Sydney Brenner

A Slot Machine, A Broken Test Tube: An Autobiography. By S.E. Luria.
Harper & Row: 1984. Pp.228. \$17.95. To be published in the UK on 31 May, £12.50.

AN autobiography allows a man the opportunity to tell all about his life and work, to reveal his secret motives and ambitions, and to give a personal view of the world and the people he has known in it. For many scientists, total self-revelation might be almost indecent; there is the professional stance of objectivity and rationality and, more to the point, there is that stuffy, critical audience of colleagues. Scientists are second only to politicians in taking themselves very seriously and in erecting deeply boring literary monuments to themselves. Perhaps only the old and very accomplished, who no longer care what people think of them, and, possibly, the slightly mad, who don't mind, can write provocatively about themselves. The reason why Jim Watson's *The Double Helix* is a marvellous book is not that it demystified the historical process of the scientific endeavour, as has been said, but rather that it tempered the drama with high comedy and, at the end, the person who emerged as the worst (as well as the best) was the author himself.

Salvador Luria, Sedgwick Professor of Biology at the Massachusetts Institute of Technology, would agree with most of this, and he sets the challenge in the preface: "I have found most biographies of scientists remarkably uninteresting and their autobiographies even more so". The book he has written is deliberately personal — a confessional account of himself and his scientific, political, literary and other interests. The treatment is not chronological and the author explains that he is replacing this by a developmental approach which he sees in existential terms, the self defining itself by creative acts of will in response to the outside world. Indeed, in the preface the reader will find a theory not only of life but also of meta-life, or autobiography.

However, the most interesting part of the book is the story of Luria's early years. He was born in 1912 in Turin, Italy, into a branch of one of the oldest Jewish families. A contemporary at school was Ugo Fano who later became a physicist and played an important role in Luria's life in giving him Max Delbrück's papers to read; I did not realize that Luria knew of Delbrück before he went to America. Luria studied medicine, spent some time in Rome, left Italy for France in 1938 and escaped to America in 1940. It is a great pity that he devotes only 19 pages of the book to this

period during which Italy and Europe underwent cataclysmic political and social changes. I would have liked to have heard more about this time of his life; given his avowed existentialist views, he should have told us more about the formative years instead of merely flitting through them. Indeed, the remainder of the historical narrative is treated in the same brief manner, and is like an abstract of an autobiography rather than the book itself.

The middle part, "The Science Path", describes his scientific work and development. All elderly molecular geneticists know of the Luria-Delbrück fluctuation experiment which proved that mutants pre-exist in bacterial cultures and do not depend on exposure to the agent used to select them. The experiment consists in measuring the variation of mutant frequency in independent experiments. Luria recounts how he got the idea at a faculty dance at Indiana University in 1943 by watching someone using a slot machine (one reference to the title of this book). The experiment was intended to refute the views of Sir Cyril Hinshelwood who did not believe in genes or mutation but only in chemical equilibria. I happen to know it did not convince him at all, because I spent several months at Oxford in 1952 and 1953 doing enough fluctuation experiments to prove to Sir Cyril that the results could not be explained by dirty test tubes. The broken test tube of the title also refers to another of Luria's experiments which led him to the discovery of the restriction phenomenon, research which has had a great impact.



The remainder of the book is about Luria's interest in literature, especially poetry, his commitment to politics and his emotional development, each considered separately, as examples of his sectorial theory of autobiography.

I found the book disappointing. Although not a contemporary, I know many of the protagonists and have lived through many of the events in science; I also know Luria and over the years have naturally formed my own opinion of him. Perhaps, like writers of autobiographies, reviewers need to be open and divulge their private judgements. There is a sense in

which this book might be even more self-revealing than the author intended. There is the Luria described, but there is also Luria the describer — a man with confident, if somewhat ponderous, judgements on all matters, noisy, irritable, ego-centric. Who else could have written the following after a reference to literature classes he conducted for science students at home?

Some time ago I received a note from a former M.I.T. student who had been in one of my classes. She reminded me that when she had told me she was planning to spend the summer after graduation learning more biochemistry I suggested that instead she read Virginia Woolf. She claims that she did follow my advice, with the result that instead of chemistry she went into business administration. Shadows of Bloomsbury! Maybe she will be another John Maynard Keynes. □

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African ancestors

C.K. Brain

One Life: An Autobiography.
By Richard E. Leakey.
Michael Joseph: 1984. Pp.207. £10.95.

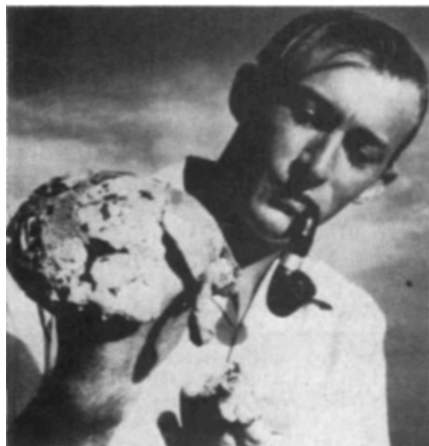
TO HAVE been born into the Leakey family of East Africa meant that, from birth, one was immersed in African antiquity, fossils and discussion of human origins. Understandably enough, Richard Leakey's first reaction was to distance himself from things academic and from the research activities of his illustrious parents, Louis and Mary. But the allure of fossil man drew him back, urging him to make a unique contribution to palaeoanthropology, on his own terms, and free of his father's shadow. How this was achieved is the story of Richard Leakey's life, related here with freshness and excitement which makes most enjoyable reading.

The road to personal discovery started in 1963 when, at the age of 19, Richard was piloting a light aircraft over the rift valley to Olduvai Gorge. Along the west side of Lake Natron he saw exposures of promising-looking sediments and before long returned to the place to establish that fossils could indeed be found in abundance there. With help from his father's National Geographic Society grant, he organized several expeditions to this Peninj site, accompanied by Glynn Isaac, who was to become codirector of the later Koobi Fora project, and Kamoya Kimeu, who in time established himself as Kenya's foremost fossil collector. This fieldwork produced a spectacular mandible of *Australopithecus boisei*, the first lower jaw of this hominid to be found in East Africa.

Richard's big chance to exercise his organizational skill came three years later, when a joint American-French-Kenyan expedition involving Clark Howell, Camille Arambourg and Louis Leakey went to the Omo valley in Ethiopia. Louis Leakey dele-

gated his son to act as his representative and as field leader of the Kenyan team, which set off in June 1967. In the course of that expedition, again while travelling by air, Richard came to see the fossiliferous sediments on the eastern side of Lake Turkana that were to prove of such immense significance.

The fossil wealth of the Lake Turkana deposits, subsequently revealed by inspection on the ground, convinced the National Geographic Society that an expedition to the area would be a rewarding enterprise. This expedition, organized and



Subjects of controversy — a youthful Richard Leakey with the 1470 skull.

led by Richard, made its headquarters at Allia Bay, and proved fruitful beyond hope — the haul of fossils was so great that each year since 1968 there has been scientific work in the area and a permanent establishment is based there.

On the second expedition of 1969 the base camp was moved to a sandy peninsula ten miles upshore known as Koobi Fora. On this expedition the young geologist, Kay Behrensmeyer, was the first to find very early stone artefacts weathering from a deposit of volcanic ash, or tuff, which could be dated. This volcanic horizon, known as the Kay Behrensmeyer Site (KBS) tuff, became the centre of a dating controversy, crucially affecting the interpretation of the fossil hominids shortly to be found at Koobi Fora. The first of these specimens, found in July 1969, was a particularly beautiful skull of a robust australopithecine. Further discoveries followed but the most significant was the 1470 skull found in July 1972 by the Kenyan, Bernard Ngeneo. This was clearly not the skull of an australopithecine: its cranial capacity was about 775 ml and, on the initial dating of the KBS tuff, it was thought to be more than 2.6 million years old. The announcement of 1470 and Richard's interpretation of it as belonging to *Homo* of such great antiquity sparked a lively controversy. It was the palaeontologist Basil Cooke who showed in 1975 that, on the evidence of fossil pigs from Koobi Fora, the KBS tuff could not be as old as first thought. Revised dating estimates put the age of the controversial 1470 skull at about 1.9 million years, where

its advanced features can be accommodated with greater confidence.

Perhaps the most striking feature of the personality portrayed in this autobiography is the driving ambition and energy behind the achievements, sharpened perhaps by the realization that Richard's life could well be a short one. In 1969, aged 25, doctors told him that his kidneys could not last more than ten years, and by 1979 his health had severely deteriorated. The situation was saved by the transplant of a kidney donated by his younger brother Phillip — this was the end of "one life", the title of the book, and beginning of another.

One of Richard's ambitions was to become Executive Director of Kenya's National Museum. But how to do it at the age of 23 and without the benefit of university training? His strategy was based on the observation that government support for the museum was low and that there was dissatisfaction with the fact that Kenyan nationals were not being trained for senior positions. Richard set about raising money, establishing an organization known as the Kenya Museum Associates with its own board of directors, which included prominent Kenyan personalities, and a formal constitution. By virtue of his position as Director of the Kenya Museum Associates, Richard attended museum board meetings and became active in the museum's administration.

The next step was to persuade a high-placed civil servant to give the board an ultimatum: either it took on Richard Leakey and made efforts to Kenyanize senior posts or else all government funding would cease! Apprehensively the museum board offered Richard a post of Administrative Officer; but rather than accept it, he insisted that it be upgraded to Administrative Director with full responsibility for the administration for the entire National Museum. The board seemed to know when it was beaten and agreed to the demand, allowing Richard to take up the post from October 1968.

This *coup d'état* approach to problems in one's life may be effective, but it tends to generate conflict and animosity. Richard was well aware of such effects, regarding them as unfortunate but unavoidable by-products of one's passage through a peopled world. Such matters aside, the life described in this autobiography is one of exuberant excitement and adventure. It tells of catching lions in the suburbs of Nairobi as a schoolboy; of narrow escapes from hungry crocodiles on the Omo River; of riding camels in search of fossils at Koobi Fora; and of finding spectacular skulls of immense interest to world science. More than this, the book illuminates a personality that has become known to millions through television programmes such as *The Making of Mankind*. □

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Measured moments

Barry Cox

Timescale: An Atlas of the Fourth

Dimension. By Nigel Calder.

Chatto & Windus/Viking: 1984. Pp.288. £12.95, \$19.95.

NIGEL Calder's unusual book provides a complete chronology of the world, starting with the first microsecond some 13,500 million years ago, and ending with the Space Shuttle.

It would obviously have been impossibly dull to do this only as a consecutive narrative, and Calder has sensibly taken several different but complementary approaches. The main section of the book (nearly 100 pages) is taken up by the "Narrative and Timescale". Because both the extent of our knowledge and the intensity of our interest steadily increase through time, Calder uses a logarithmic scale. So, after mention of the first million years that encompassed the birth of the Universe, each double-page spread deals with progressively smaller bites from the cake of time, starting with 3,500 million years and passing through 6,000 years to end with the past eight years. (But the author has not allowed himself to become the slave of this format, for the text runs continuously from spread to spread.)

Though the narrative that accompanies this roller-coaster ride through history is always clear and coherent, it can inevitably make only passing reference to many significant events. Calder has therefore added a reference index, about 100 pages long, in which topics are elaborated or added. This includes over 900 entries, most of which are given dates for their origin or extent in time, and are cross-referenced — e.g. blue-green algae (bacteria) est. 1600 Myr, *see* life on Earth; stromatolites. The entries range in length from one line to three pages, and many provide useful references for further reading.

Calder's third approach is to give eight pages of maps, which show the various stages of continental drift, the climate and geography of the Ice Age maximum, and the dispersal patterns of the races, languages and techniques of mankind.

In the sixty-page introductory "Overview", Calder puts the whole chronological enterprise into the historical perspective of its discovery. This, too, is written in a stimulating and provocative style — for example, he suggests that the master of the planet is grass, which has seduced its human slaves into cultivating, protecting and feeding it. We are, then, the puppets not only of our selfish genes, but also of our selfish grains. Calder's book is both enjoyable and useful — not a common combination. □

Barry Cox is Head of the Zoology Department at King's College, University of London.

Believing in hunters and gatherers

John E. Pfeiffer

Historical Atlas of World Mythology.

Vol.1, *The Way of the Animal Powers*.
By Joseph Campbell.

Alfred van der Marck Editions, San Francisco (distributed by Harper & Row): 1984. Pp.304. \$75. To be published in the UK on 30 June by Times Books, £35.

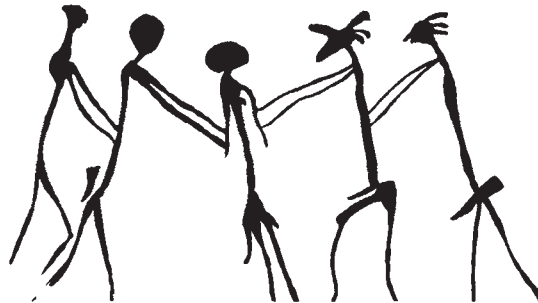
MYTHS are taken more seriously nowadays than was the case two world wars and a holocaust ago, when the distinction between primitive and civilized cultures seemed more clear-cut. No longer viewed as tall tales, as the superstitions of tribal and pre-tribal peoples in faraway places, myths are appreciated as highly structured belief systems serving chiefly to hold societies together. For more than half a century these systems have been the overriding concern of Joseph Campbell, Professor Emeritus of Religion at Sarah Lawrence College in New York, with the past decade or so devoted to his major work: the compilation of a historical atlas of world mythology, which will appear in four volumes over the next two years.

Volume 1, *The Way of the Animal Powers*, deals with the origins of myth-making during hunter-gatherer times. It is far more than an atlas, if that implies a book consisting predominantly of maps. There are indeed plenty of maps, 50 to be precise, but they supplement an extensive text which makes up the bulk of the book and in which Campbell confronts the most formidable question of cultural evolution — of what possible value could myth be to the human animal, a minority species engaged to the hilt in competition with other predators for food and living space? After all, our ancestors endured for ages and managed to increase their numbers appreciably without the benefit of myth, at least as far as we can tell from the archaeological record.

Hominids, members of the human family, arose in Africa five or more million years ago, stayed there for at least three to four million years, and then spread to Europe and Asia and, most recently, to Australia and the New World. This process is illustrated in a series of informative maps, which also indicate glacial advances and retreats as well as progressive stages in the art of tool-making. The first signs of myth, the first hints that the human species was off on a new tack, date back 50,000 to 100,000 years, only yesterday on the evolutionary time scale. The notion that death is a beginning not an ending, that we live on invisibly in an afterlife, has been traced to the earliest known burials in western Europe, Neanderthals laid to rest on their sides as if asleep, and with mint-condition

tools and provisions for their journeys to another world.

An explosion of myth, what Campbell calls "the awakening of awe", came not long afterwards with the passing of the Neanderthals and the emergence of our kind of hominid, euphemistically known as doubly wise *Homo sapiens sapiens*.



Art of African hunter-gatherers, possibly depicting the ritual abduction of a girl (by animal-headed figures on the right, resisted by the figures on the left). The illustration is taken from A. R. Willcox's *The Rock Art of Africa*, a scholarly and well-illustrated book recently published by Croom Helm in Britain and Holmes & Meier in the United States. Prices are £45 and \$69.50, respectively.

Ceremony appeared as a major feature of prehistoric life, increasingly elaborate performances staged deep underground in the limestone caves of western Europe. Only the art remains, the backdrops — vestige figures representing the world's first "art movement" which culminated 20,000 to 10,000 years ago with superb animals, bison and mammoths and other big game, painted and engraved on cave walls. It is as if all we had from the times of Gothic cathedrals were stained-glass windows and graven gargoyle images.

According to Campbell, no single cause can explain the spectacular rise of myth. For one thing, there was crowding, individual against individual, with soaring population densities, and myth was embodied in ceremonies designed to create closer tribal ties. The related need to feed more people, to kill magnificent animals on a mass basis, resulted in an additional conflict of conscience "with a compensatory mythology . . . of a bonding covenant between the animal and human communities". Further factors contributing to "the creative explosion" included the landscape itself with its deep caverns "inspiring religious awe", the arrival of modern human beings, and the "visionary trance-seizures" of shamans who tapped unconscious forces in devising healing rites and initiations.

Campbell marshals ethnography as well as archaeology to support his analyses. He covers the world in describing the living folklore of present-day and recent hunter-gatherers, including the desert-dwelling Australian aborigines and Kalahari Bushmen, Eskimos, Tierra del Fuegians and Andamanese Islanders, forest peoples such as the Zaire pygmies and the recently discovered Tasaday of the Philippines — all complete with maps presenting geographical distributions of art styles and cults, and a unique index of myth motifs from "Aardvarks" to "Yucca fruits".

I only wish that in the process of bringing all of this information together, a prodigious task, Campbell had achieved a

sharper focus in organizing his book. All the basic findings and ideas are there, but so dispersed that their net impact is somewhat weakened. On the other hand, he has produced an outstanding survey of hunter-gatherer beliefs, and a much-needed reference work. We can look forward to his forthcoming volumes on the nature of

myths associated with agricultural societies, on the first civilizations, and on our own uncertain and increasingly complicated times. □

John Pfeiffer's most recent book is *The Creative Explosion: An Enquiry into the Origins of Art and Religion* (Harper & Row, 1982). He is currently completing a fourth edition of his textbook, *The Emergence of Man*.

Nature of idealism

W.F. Bynum

The Philosophical Naturalists: Themes in Early Nineteenth-Century British Biology.

By Philip F. Rehbock.

University of Wisconsin Press: 1983.

Pp.281. \$30, £25.50.

UNTIL a decade or so ago, historians of science seemed often to assume that the view of nature which Darwin's *Origin of Species* challenged was deeply rooted in a lingering, cautious Paleyite emphasis on special creation, individual adaptation and the argument from design. Romantic biology and transcendental anatomy were looked upon as largely Continental concerns which at best only marginally influenced empirically-minded British naturalists.

More recently, however, research by scholars such as the late Dov Ospovat, Adrian Desmond and Janet Browne has demonstrated the inadequacy of that view. Far from being ignored, "philosophical biology" (as it might be called) was actively pursued by a number of leading British zoologists, botanists and anatomists. From the 1820s, many of the major themes of Continental biology were assimilated into British natural history: a continuing preoccupation with the "chain of being" and with an underlying unity of plan in plants and animals; concern with biological types rather than individual species; a willingness

to speculate; and an explicit philosophical idealism.

Philip Rehbock's *The Philosophical Naturalists* can now be added to this growing historical literature, and the first half of his book, on "the idealist approach to nature", offers an excellent summary of the relationship between British and Continental biology in the second quarter of the nineteenth century. Rehbock is not the first to note that Edinburgh was the cradle of much philosophical biology in Britain. Robert Knox, Robert Edmond Grant, Richard Owen, Edward Forbes, John Goodsir: these and several other apostles of the "new" biology of the 1820s and 1830s shared a common intellectual heritage in the Scottish capital. Rehbock focuses on Knox (the unfortunate surgeon and anatomy teacher who received the victims of Burke and Hare), using his original writings and translations as a vehicle for expounding the main features of British transcendentalism. Owen and Goodsir receive rather more cursory treatment.

The second half of the book deals more comprehensively with the curious and often obscure biogeographical work of Edward Forbes, the attractive and personable naturalist who died in his prime, before the implications of his speculative vision of nature could be fully worked out. Forbes's research on what he called "centres of creation", and their connection with presently observed plant and animal distribution, was much discussed in the 1840s, although it also involved him in one minor and one major priority dispute with Charles Lyell and Hewett Watson respectively.

Rehbock is a reliable guide to his chosen themes, and his book amply exposes the impact of philosophical idealism on pre-Darwinian natural science in Britain. It is not, however, a comprehensive analysis of the subject. The author is good on the Edinburgh scene, but weak on the London flowering of transcendentalism during the 1840s, when Owen, Grant, J.H. Green and others were active at University College, the Royal College of Surgeons and other London institutions. There is little attempt to place his major figures into their social, political or professional contexts. Rehbock also fails to assess (or even to cite) much relevant secondary literature, suggesting that little has been done on the book since 1975, when the PhD thesis on which it is based was completed. Occasional slips such as Humphrey [sic] Davy and Alfred Russell [sic] Wallace also mar the text. Nevertheless, publication of *The Philosophical Naturalists* is to be welcomed as another contribution to the understanding of the complex biological scene which flourished in Britain during the very decades in which Darwin was preparing his own statement.

W.F. Bynum is at the Wellcome Institute for the History of Medicine, London.

No stone unturned

Keith Bell

It Began with a Stone: A History of Geology from the Stone Age to the Age of Plate Tectonics.

By Henry Faul and Carol Faul.

Wiley: 1984. Pp.270. Hbk \$38.95, £35; pbk \$19.95, £16.

CHARTING the development of geology from antiquity through to post-Wegenerian times is a formidable task. *It Began with a Stone* attempts to do just that. Packed with factual information, written in a breezy style and coupled to an extensive bibliography, it documents most of the highlights in the history of the earth sciences.

In this, the book is a success. Topics are numerous and diverse; not only is the classical age of geology covered in detail, but included are such lesser known subjects as the significance of French discoveries and theories in the seventeenth and eighteenth centuries, the establishment of the US State Surveys and even the fate of geologists during the American Civil War. Important developments in the earth sciences are nicely dovetailed into both a geographical and intellectual context.

The fragmented nature of geology started to disappear with the age of travel. Lyell's visit to eastern North America, his meeting with the cranky yet brilliant James Hall, Dana's and Wilkes's journey around the world, and the opening of the American West played important roles in the consolidation of new ideas and the provision of a solid basis for the relatively young science. This backdrop, together with a cast as intelligent, as colourful and as scurrilous as one could find, are among the fascinating material included in the Fauls' book.

It is difficult to compare this book with others of similar type. *The Birth and Development of the Geological Sciences*, published in 1938, although a more scholarly and sophisticated work, stops at the turn of this century and lacks the freshness and excitement of the Fauls' book. The style of delivery in the latter does, however, tend to be frenetic — a more relaxed pace would have helped readers absorb the bewildering array of information contained in the text.

The book can be read at two levels. For idle browsing, the many interesting and amusing asides can be savoured with relish. For more serious reading, the wealth of information provides a more detailed coverage than has been available until now. Henry Faul died before the manuscript was completed. Anyone who knew Henry will recognize his style, his perception and his scholarship — this book is a fitting memorial. □

Keith Bell is a Professor in the Department of Geology, Carleton University, Ottawa.

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By J. A. Diment et al.

1984. 0 565 00937 0. Paperback £30.00.

Publications Sales, British Museum (Natural History), Cromwell Road, London SW7 5BD.

Rich man, poor man

David L. Hull

Just Before the Origin: Alfred Wallace's Theory of Evolution. By John Langdon Brooks. Columbia University Press: 1984. Pp.284. \$30 (United States), \$39 (elsewhere).
Alfred Russel Wallace: The Great Naturalist who Challenged the Orthodoxy which He and Darwin had Established. By Harry Clements. Hutchinson: 1983. Pp.215. £8.95.

IN spite of striking parallels, the lives of Charles Darwin and Alfred Russel Wallace could not have been more different. Darwin was born into comfort and security, attended the best schools, accompanied Captain Fitzroy on the *Beagle* as a companion-naturalist, and upon his return settled down to a remarkably uneventful life — walks in his garden at Down, bouts of flatulence, an occasional visit to a spa to nurse his mysterious illness, and of course the publication of book after book on topics as diverse as the power of movement in plants and the formation of vegetable mould by worms.

Wallace was born in near poverty, was farmed out to an older brother in London at the age of 14 after only six years of schooling, and held down a succession of jobs until his brother died leaving him a bit of money. Wallace immediately set sail for the Amazon. A year later a second brother joined him. Both men came down with yellow fever and the brother died. After four years in the jungle, Wallace sailed for home with his precious collections. *En route* the ship caught fire and sank. After ten days on the open sea in a small boat, Wallace was saved, but four years of labour went down with the ship. No sooner did Wallace find his way to England than he began to plan for a second voyage, this time to the Malay Archipelago. It was here, while confined to his bed with a fever, that the idea of natural selection flashed across his brain.

Dozens of biographies have been written of Darwin. Only a handful of books have chronicled Wallace's even more fascinating life, and most of these have treated Wallace as if he were Darwin's moon, shining only in Darwin's reflected brilliance. The volumes by Brooks and Clements are the latest additions to this small literature. Brooks's book is primarily a scientific biography, tracing the genesis of Wallace's ideas on organic change from his reading of Chambers's infamous *Vestiges of the Natural History of Creation* (1844) to the publication of the joint Darwin-Wallace papers in 1858.

Clements's biography is a good deal less technical and is more concerned with Wallace's later life, especially his championing of a variety of unorthodox scientific and social causes. Because Clements himself practised for many years his own brand of osteopathic nature cure,

is his inevitable indictment of Darwin's treatment of Wallace. As the story is usually told, Darwin became persuaded that species evolve sometime in 1837, stumbled across natural selection in 1838, and worked on his theory for the next 20 years. In 1855 he noticed a paper published by Wallace arguing that new species always come into existence in close proximity in both space and time with pre-existing closely allied species but convinced himself that Wallace intended creation, not transmutation. This paper did, however, contribute to Darwin's decision to begin work on his Big Book. Darwin even corresponded with Wallace, informing him that he too had been working on the species question.

As a working-class boy, Wallace knew no one. His 1855 paper had been totally ignored, at least so he thought. His new manuscript setting out evolution by means of natural selection was even more speculative than the first. How to get his fellow naturalists to notice? How could he prevent them from dismissing it with derision? Darwin was his only hope. Thus, on 18 June, 1858, Darwin received Wallace's manuscript that came like a "bolt from the blue". Darwin promptly sent the manuscript to Charles Lyell, as Wallace had requested, accompanied by a letter asking for advice about what he should do. He wanted to behave honourably, but he also did not want to be robbed of priority. Lyell and J. D. Hooker suggested that Wallace's paper be read along with a couple of short pieces by Darwin before the Linnean Society and then published in its journal, and this was the course of action that was eventually taken — without consulting Wallace. A year later Darwin published his *Origin of Species*.

Darwin was the first to admit that he deserved no special priority in the matter of the transmutation of species. A large number of workers before him, including his own grandfather, had advocated evolution of sorts, but Darwin did claim priority for natural selection. Needless to say, numerous anticipations have been uncovered since, and Loren Eiseley has even argued that Darwin stole the idea of natural selection from his friend Edward Blyth. That Blyth himself thought otherwise is beside the point. Brooks goes even further. A third pillar of Darwin's theory was his Principle of Divergence, a suggested mechanism for the subdivision of single ancestral species into two or more daughter species. Brooks claims that Darwin stole his later formulation of this principle from Wallace. Brooks argues that the appear-

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"A.R. Wallace admiring *Eremurus robustus* (about 1905)". The picture and caption are reproduced from Vol.II of *Alfred Russel Wallace: Letters and Reminiscences* by James Marchant, published by Cassell in 1916.

he is more sympathetic to Wallace's heterodox views than other authors have been in the past.

The most valuable part of Brooks's book is his detailed discussion of the genesis of Wallace's views on evolution and biogeography. In this connection, Wallace had one major advantage over Darwin. Wallace was persuaded that species evolve prior to leaving on his voyages, while Darwin did not abandon creationist beliefs until after his return. Thus, Wallace was able to gather data with an eye to his evolutionary hypothesis.

The weakest part of Brooks's discussion

ance of Wallace's 1855 paper not only caused Darwin to start his species book but also provided him with his tree simile. This latter contention is clearly false because Darwin included two drawings of an irregularly branching "tree of life" in his 1837 notebooks. More importantly, Brooks claims that Darwin received Wallace's paper on 18 May, 1858, not 18 June. As Brooks construes the evidence, Darwin immediately sat down to write Lyell a letter, but did not mail it. Instead, he went back to re-read Wallace's 1855 paper and then proceeded to re-write his discussion of the Principle of Divergence. Only after he had reported the completion of this section did he send his letter to Lyell along with Wallace's manuscript. Darwin himself dated the letter only "18th". According to Brooks, the pencilled notation "June 1858" was added later and indicates when Lyell received the letter, not when Darwin sent it.

I suppose the proper thing for Darwin to have done when he received Wallace's manuscript was to forward it to Lyell as requested and then to write Wallace in Malay for permission to publish it. Six months to a year later, the time it would have taken Darwin to receive an answer from Wallace, he could then have seen the paper into print. If he had, I suggest that the history of evolutionary theory and the apportioning of credit would not have changed in the least. Darwin's critics could then complain at Darwin's inexcusable delay in publishing Wallace's paper. Scientists are very interested in priority and rarely miss a chance to engage in vicious priority disputes. For once two scientists declined the opportunity, but commentators such as Brooks will have none of it. They turn over every bit of nastiness that they can discover or invent. I have no idea what took place in Down between 18 May and 18 June in 1858, but if the choice is between Brooks's circumstantial evidence and the testimony of a long life lived in the public spotlight, I am inclined to go along with Wallace and opt for Darwin.

In Clements's book Wallace is the sun, and Darwin is only a dim though benign spectre circling in the distance. As Clements portrays Wallace, he was an honourable and decent, though somewhat unworldly, man. Darwin consciously built a reputation as a serious scientist before declaring himself on such a controversial subject as evolution. Wallace was thrust into the public eye immediately upon his return from his second trip. A more judicious man might have followed Darwin and written a series of technical monographs elaborating his views on the transmutation of species. He did publish works of this sort, but he also came out in favour of supernaturalism, phrenology, mesmerism, the nationalization of land, and eventually socialism, while opposing vaccination, vivisection and any form of militarism. Wallace's fellow evolutionists were not pleased. Upon receipt of a paper by

Wallace arguing for the scientific validity of certain reports of supernatural phenomena, Huxley replied that he had "never cared for gossip, and disembodied gossip, such as these worthy ghosts supply their friends with, is no more interesting to me than any other" (p.114).

When it came to human beings, Wallace was not a Social Darwinist. He thought that most of the illnesses of the time were due to the conditions under which people had to live, and he urged radical social change to alleviate them. He was less enthusiastic about intervening in non-social phenomena. He was highly critical of the claims that the medical establishment was making at the time for vaccination. He thought that once people lived in healthy surroundings with ample food and clean air, vaccination would be unnecessary. A healthy person need not fear being attacked by disease. At the very least, Wallace argued that the figures available indicated that vaccination was causing more illness than it was preventing. For both moral and economic reasons, Wallace also favoured vegetarianism, but he himself was unable to practise it, especially after a diet of hot water and lean meat advocated by a Dr

Salisbury cured him of his chronic fevers.

My main reservation about Clements's book is his repeated contrast between Darwin, who "kept within the narrow limits of his natural selection orbit" (p.xix) and the more pluralistic Wallace, who eventually came to believe that no naturalistic explanation could be given of the origin of either life or mind. To the contrary, Wallace was the one who argued for the all-sufficiency of natural selection, while Darwin acknowledged subsidiary roles for a variety of additional forces. When Wallace became convinced that natural selection was inadequate to account for the superabundant powers of the human brain, he had no auxiliary naturalistic hypotheses to fall back on and was forced to posit a supernatural agency.

For anyone who wants to follow the genesis of Wallace's theory of evolution, the early chapters of Brooks's book are helpful. For anyone wishing to understand Wallace as a total person, Clements's biography is a good place to begin. □

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Eye of the beholder

Jonathan Silvertown's textbook, Introduction to Plant Population Ecology, was published by Longman in November 1982. To date some ten reviews have appeared, with more still to come. No one who has written a book and then followed the subsequent reviews will be surprised that reviewers found different things in the book:

On the one hand . . .

"Ecological curiosities — parasitic angiosperms, carnivorous plants, the vine habit — have been neglected." (*Ecology*)

"Another annoying problem with the book is that the 'summary' section at the end of each chapter seems superfluous . . ." (*Ecology*)

"In places the text is extremely condensed and may cause some difficulty, especially for the less numerate student." (*Ann. Bot.*)

"There are, however, some significant omissions. For example, the reader might be excused for concluding that pathogens have no effect on births and deaths of plants and that herbivores have little effect." (*Times Higher Education Supplement*)

"Subjects such as natural selection (p.5) and seed and pollen movement (p.22) are regarded as beyond the scope of the book . . ." (*J. appl. Ecol.*)

. . . but then, on the other

"The vine of evergreen tropical forest whose oskars store food reserves in large tubers and whose central stem suddenly 'sprints' upwards to the tree canopy . . . provides a splendid focus for a discussion of dormancy." (*J. biol. Educ.*)

"A particularly useful feature is the use of summaries at the end of each chapter. . ." (*J. biol. Educ.*)

"The book will be readily understood by those with little background in mathematics." (*Times Higher Education Supplement*)

"Though it is not apparent from the list of contents the role of pathogens and animal predators is dealt with in relevant sections." (*Ann. Bot.*)

"Silvertown makes many pertinent comments on the work he is quoting, and always has an eye for the evolutionary implications of the subject under discussion." (*Biologist*)

The mischief maker

J.O. Marsh

The Demon in the Aether: The Story of James Clerk Maxwell.

By Martin Goldman.

Paul Harris, 40 York Place, Edinburgh: 1983. Pp.224. £18.

JAMES Clerk Maxwell was more an imp in the underdrawings than a demon in the aether. True, his mischievous activity so undermined classical physics as to bring it to ruins, but that was not until 30 years after his death. Demon or imp, Maxwell remains an insubstantial figure behind the pages of Goldman's biography.

The facts of Maxwell's life have been established by other scholars. His father devoted most of his married life to developing and improving the family estate, Glenlair in Galloway. James, the only surviving child of the marriage, was educated by his mother until, when he was eight, she died. His father continued the schooling initially by having James assist him with his improvement schemes and later by employing a tutor. The tutor was a disaster and, at the age of ten, James was sent to live with his aunts so that he could attend the Edinburgh Academy. There he made two lifelong friends, Lewis Campbell and Peter Guthrie Tait, and gained the nickname "Dafty".

After six years of learning classics at the Academy, Maxwell entered Edinburgh University. He remained there for three years (perhaps to stay near his father), studying mathematics under Phillip Kelland, philosophy under William Hamilton (not the Irish mathematician) and natural philosophy under James Forbes. Then on to Cambridge and the "Public Service" examination, the maths tripos. He was second in the tripos to Routh but equal first with him in the unofficial physics examination, the Smith's prize.

After Cambridge, Maxwell's career was spectacular only by his early death. He spent two years as Scholar and then Fellow of Trinity College, four years as Professor of Natural Philosophy at Marischal College, Aberdeen, five years at King's College, London, and then six years retirement at Glenlair (completing his father's schemes on a considerably reduced scale). He failed in an application to become Principal of St Andrews in 1868 and was third choice to direct the new Cavendish Laboratory at Cambridge. However, the two preferred candidates (Kelvin and Helmholtz) declined and Maxwell was appointed Cavendish Professor of Experimental Physics in 1871. He died of stomach cancer eight years later.

Maxwell's official biography was written by his Academy friend, Lewis Campbell, and his Cavendish Laboratory assistant, William Garnett, and first published in 1882. This six-hundred page classic of Vic-

torian sentimental hagiography is the main source for the ten biographical chapters of Goldman's book. By cutting extensive quotations to "juicy" paragraphs, by adding a bit of gossip about Maxwell's wife and by suggesting that Maxwell's religious belief was conventional "religiosity", Goldman presents Campbell and Garnett's Maxwell suitably repackaged for our modern Victorian age.

In the 1882 biography, William Garnett described Maxwell's scientific contributions under seven headings: experiments on colour vision and other contributions to optics; investigations respecting elastic solids; pure geometry; mechanics; Saturn's Rings; Faraday's lines of force and Maxwell's theory of the electromagnetic field; and molecular physics. Garnett stated that his contemporaries judged the latter two as most important and in this posterity has shown them to be correct, though not in the way they might have expected. Maxwell's electromagnetic theory led directly (not via the Michelson-Morley experiment) to Einstein's theory of special relativity, and his molecular physics (dynamical theory of gases) led to statistical physics and quantum mechanics.

Goldman devotes four chapters to Maxwell's scientific work: one each to the dynamical theory of gases and electromagnetic theory, one to the revolutionary consequences of these theories and one to the rest of Maxwell's scientific work. Apart from the latter, which is little more than the catalogue above, each of these accounts is

seriously flawed. So, in the chapter on the dynamical theory, Goldman claims that the analytical methods of Fourier are "an abstract mathematical technique, far from the geometrical methods 'normally' associated with Maxwell" (p.110). This is nonsense. Part of Maxwell's genius lay in his ability to switch from geometrical to analytical methods and back, and this he did frequently and to great effect.

In the chapter on electromagnetism, Goldman states "It seems quite remarkable that Maxwell's book, which even today is a model of precision and clarity, should have appeared murky and impenetrable to his contemporaries" (p.159). Three pages later Goldman himself identifies the great problem with Maxwell's theory: "Underlying the whole theory was the basic ambiguity of the nature of charge" (p.163).

Goldman is either unaware of, or has ignored, the work published over the past ten years of at least a dozen scholars. Attention to that literature might have helped him avoid many errors, but I doubt if anything would have deflected him from the triteness of his conclusions:

As a boy he electroplated beetles and played marbles ('bools') as a man he unified electromagnetism and founded statistical mechanics. There is a wholeness in the circularity and immutability of his interests [p.195]. □

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Public knowledge

Jonathan C. Howard

Aristotle to Zoos: A Philosophical Dictionary of Biology.

By P.B. and J.S. Medawar.

Weidenfeld & Nicolson/Harvard University Press: 1984. Pp.305. £15, \$18.50.

IT IS necessary only to open the Sunday papers to discover that the educated man in the street has recently adopted biology as a topic for generalized opinion and discussion. It is hardly surprising that biology should be the first science whose basic concepts enjoy universal currency. Biology alone among the sciences has been taught to all schoolchildren in the Western world for over a generation. The primitive traditions underlying the organization of schools have been allowed to deny most girls a proper education in mathematics and the physical sciences. As the girls and the physical sciences have lost from this mad policy, so biology has gained. Minds cultivated in biology are now as common among women as among men. In the biological sciences it is therefore no surprise, only a pleasure, to find a husband and wife sharing the writing of a book, and it is

especially apt that the book should be a work intended to enlighten still further the biologically literate general public.

Aristotle to Zoos is an odd book. Ostensibly based on Voltaire's *Philosophical Dictionary*, the Medawars have used the format as an excuse to write as much or as little as they wanted on whatever biological topics they fancied. This is, of course, a recipe for self-indulgence, and the book is not entirely free from this vice. Turning to the entry on Aristotle, for example, the startled reader discovers that for some reason the Medawars have it in for the old boy in a big way, quirkily preferring Coleridge as a superior alternative, and muttering about monkeys on a typewriter. I suspect that Sir Peter Medawar may have allowed his distaste for authors who write too much to get the better of his critical judgement. I remember a masterly Herbert Spencer Lecture given by Medawar in Oxford some years ago. Medawar had borrowed Spencer's gigantic *System of Philosophy* from the Royal Society library and transported it to the lecture theatre in Oxford in order to illustrate his gleeful pronouncement that he himself had been obliged to cut the pages. His disparaging view of Spencer was shared by the Dean of Westminster, who noted in 1904, while denying a request to bury Spencer in the Abbey,

"when I ask with what important achievement in philosophy or in natural science, or with what permanent contribution to thought his name is destined to be connected, I meet with no satisfactory reply". At face value, this seems to be alarmingly close to the Medawars' view of Aristotle!

Experienced Medawar readers will recognize that a good deal of the serious matter of the dictionary represents Sir Peter's scientific preoccupations of many years standing — demography, growth and form, the immune system and so on. These little essays are beautifully written, trenchant, witty and informative. They are also so erratic in level as to provoke me into articulating the question I had vowed, before writing this review, not to ask. For whom are these essays written? For example, "Growth, Laws of Biological" has a full-page table giving the equations and analytical properties of three growth functions, while "Population, Growth and Control" has a little box showing what an exponential series is. It probably doesn't matter. After all if some of the subject matter of biology lends itself to elegant mathematical treatment, then why should not the numerate man in the street be given the pleasure of enjoying it?

In the same context, an odd feature of the book is the evidence that its authors do not have a particularly high regard for the intellectual pretensions of the very members of the lay public who must be expected to buy it in largest numbers. Twice this group is identified as that to which the structural formula of water represents the upper limit of scientific knowledge. I do not trust this attitude. Who knows how the lay public, deprived of precise understanding, perceives science? What is certain is that it does not want to have its head bitten off by the Medawars because it knows only that H_2O is water, or because it does not yet know that man is not an aggressive animal, or that you can't change human nature. It does not help to be told merely that "educated people do not have to refer to ethnological papers before rebutting these trite propositions. Indeed, such phrases are now almost universally taken to mark an especially low

level in conversation or discussion". I can only suppose that these strictures are intended to frighten the ignoramus into silence.

But it is best not to worry, and rather enjoy the lovely prose and the tough precise intelligence. This is not the place to hunt for oncogenes, homeotic mutants or other heroic manifestations of the trend end of modern molecular biology. Rather, *Aristotle to Zoos* is more like a guided tour through an antiquary's collection of unusual, funny, embarrassing or lovely things chosen for their intrinsic interest or on a whim rather than for topicality or information alone. In Voltaire's *Dictionary* the whimsical titles and strange oblique manner were the disguises of a robust and effective attack on the hypocrisy, intellectual poverty and temporal tyranny of the Catholic Church. If a central informing theme is to be found in the Medawars' dictionary, it is an appeal for a disciplined and critical mind.

A final comment, suggested appropriately by the essay on zoos. Experimental biologists are often called on to abuse animals in the course of their work. These abuses are both sanctioned and limited by the laws which cover cruelty to animals. It is important to realize that, in Britain, the Cruelty to Animals Act (1876) is explicitly intended to *permit* cruelty to animals. Without a doubt, this licensed cruelty to animals takes its toll on the scientist's sensibilities, on his ability to judge the consequences of his experiment by what one might call "normal" humane standards. Just because our animal experimentation is regulated by law, and law which is necessarily diffuse and imprecise in application, it is difficult for the scientist to retain a sense of primary obligation to the animal rather than to the law or to the experiment. Both in "Zoos", and more explicitly in the superbly judged and eloquent essay "Animals and Human Obligations", the Medawars show that they have managed, after a lifetime in experimental biology, to keep their sensibilities intact. □

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Thoughts from the High Table

Steven Rose

The Synergism Hypothesis: A Theory of Progressive Evolution.

By Peter A. Corning.

Blond & Briggs/McGraw-Hill: 1983.

Pp.492. Hbk £15, \$19.95;

pbk \$12.95.

CONFRONTING the ultimate question, the secret of life, the universe and everything, that well-known text *A Hitchhiker's Guide to the Galaxy* responds simply "42". Dr Corning's response is *The Synergism Hypothesis* but, unlike the *Guide*, he takes a full 492 pages of eclectic and autodidactic argument to expound a thesis which he claims embraces everything from biological evolution to how to run hospitals in California, taking in *en route* cost-benefit analyses of the relative merits of the political systems of Iran and Mexico, and cooperative phenomena in the synthesis of proteins. It is at once evident that in *The Synergism Hypothesis* we are confronted with a book that its author and publishers wish us to see as a Great Event. Faced with such a range of subject matter and an author who we are told is "one of the pioneers in applying a biological perspective to the social sciences" how is a poor Cambridge empiricist like the present reviewer, constrained to crawling along the frontiers of knowledge with a hand-lens, and taught to eschew Grand Theory, to cope?

Dr Corning, as we might imagine, has few doubts as to the importance of what he has achieved — "like Darwin's theory, properly understood, my theory makes only one unequivocal prediction", he informs us with no false modesty (p.392). One's sense of awe is only slightly quenched to read on as follows: "that the future cannot be predicted with certainty because the process is not linear or deterministic . . .". Well yes, but Darwin had just a little more to say than that, or we would not still be reading him today. Dr Corning, however, sees himself firmly seated at High Table with the intellectual giants of the past 2,500 years, praising Plato and Durkheim here, criticizing Marx and Darwin there, mapping his own ideological descent with a scent-marking of faint acclaims and sharp disapprovals.

So what is the Synergism Hypothesis? "Functional synergism is so much a part of our daily lives that we generally take it for granted" (p.228). Well, thanks. But is it new? "Plato and Aristotle understood the synergism principle; so did Adam Smith" (p.229). So why do we read Dr Corning? To tell us that we can see synergism at work when we "Imagine a scissors with only one blade, a tweezers with one claw . . . a broken drinking glass . . . an electric appli-

IMAGE
UNAVAILABLE FOR
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REASONS

ance during a power outage" (p.230). Synergism is in the food we eat, the baking of a lemon pie, personal health, the telephone system, insurance, shopping centres, multiple movie theatres (p.233). So that's what Adam Smith has in common with a supermarket?

Beneath his grandiose rhetoric and camouflaged by his heavy reference list, Dr Corning is calling attention to the modest but unfortunately not self-evident statement that reductionism is an inadequate programme for the scientific understanding of living organisms or the societies they construct. Although it is not clear why the author thinks he has contributed significantly to the debate over the limits to the reductionist programme, there is no doubt that his book has been written in reaction to claims made even more stridently than his own — those of sociobiology. E.O. Wilson's ludicrous claim that "The development of fundamental theory in sociology must await the full neuronal explanation of the brain" stands, an epigram contrasted with others by Durkheim and Gould, at the head of one major chapter. Dawkins's "lumbering robots" programmed by those misbegotten "selfish genes" lurk wolfishly in Corning's pages to be stripped yet again of their skins to reveal the sheep they really are.

Complex wholes are not reducible to ontologically prior parts; systems have properties which are not dissociable into, or strictly predictable from, the units of which they are composed. New properties emerge with complexity, and genes should no more be described as selfish or aggressive than should humans be regarded as subject to Van der Waal's forces or Brownian motion. Laws of motion descriptive of one level of organization of matter are not translatable, holus-bolus, to another. That these statements are not self-evident is due to the ideological power of reductionism, not least within the pages of *Nature*. Therefore, I must, in principle, welcome Dr Corning to the side of the good and the true who fight the brave fight against reductionism.

However, mine enemy's enemy is not always to be seen as unequivocally clear-headed and right-minded. In his eagerness to defeat the reductionist myth, Dr Corning elevates synergism itself to the great organizing principle of nature much as Engels once did for the dialectic. Oddly *The Dialectics of Nature* does not appear to be part of Dr Corning's otherwise omnivorous reading, albeit his list of examples of synergism reads uneasily like Engels's claims to find the transformation of quantity into quality in the boiling of water, and the interpenetration of opposites in the north and south poles of a magnet.

Despite Dr Corning's clarity in avoiding the trap of reducing individual social actions to the mere motions of molecules, he oddly fails to avoid the trap of seeing society as composed of individuals whose market-like relationships conform to some

cybernetic principle or other. Whether individuals choose to act socially, he implies, is their own affair — as if they at least were free. Faced with the problems this might entail, he weakly invokes Sperry's principle of downward causation as if this might spring the trap. The consequence is that whilst his early chapters on Darwin, progressive evolution and interactionism are merely platitudinous and longwinded, his final chapter on a "general theory of politics" is downright inadequate. A theory of politics which has no place for conflict — of class, gender or race — and which sees no theoretical difference between socialism and capitalism, is frankly out of place in anything except, apparently, a Stanford Political Science class. It

is in this chapter that Dr Corning compares his two Californian hospitals, one cybernetically run, "lean, highly efficient" and generating a satisfactory profit; the second lax, with a "chit-chat culture" which turns a loss to its investors. There is no doubt which Dr Corning prefers. But his account fails to tell us which of these two hospitals has a better patient recovery rate, and in which of the hospitals the patients feel happiest. Could there just be something missing from his Grand Unified Theory? □

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Between Brussels and Westminster

Eric Ashby

EEC Environmental Policy and Britain: An Essay and a Handbook.

By Nigel Haigh.

Environmental Data Services, Unit 24, Finsbury Business Centre, 40 Bowling Green Lane, London: 1984. Pp.324. Pbk £12.95, \$25.

The Pollution Control Policy of the European Communities, 2nd Edn.

By Stanley P. Johnson.

Graham & Trotman, Sterling House, 66 Wilton Road, London: 1983. Pp.244. £18.

"AS BEFITS the genius of Europe, particular attention will be given to intangible values and to protecting the environment. . .". This burst of rhetoric was issued by the heads of state or government in the European Community, when they met in 1972. It is the foundation for an environmental policy for Europe. A weak foundation, in the opinion of some lawyers, for the legal basis of the European Community is the Treaty of Rome; the purpose of the Treaty is to establish free trade between member states. To this end the member states agree to approximate (or "harmonize") their national laws in so far as they "directly affect the establishment or functioning of the common market". Laws to protect the environment are, so these lawyers say, irrelevant to the Treaty unless it can be demonstrated that they "directly" affect trade.

This is no legalistic quibble. An important principle is at stake. Every item of Community law agreed to by a member state involves a corresponding surrender of sovereignty by that state. Directives from the Community, once agreed, have the force of international law. Therefore if Britain acquiesces in some Community law to protect the environment and which has no direct effect on the functioning of the

common market, there may be a risk (to quote the words of one of Britain's law lords) of "a creeping surrender of our national sovereignty in almost unlimited fields of law". Well, we have taken the risk.

The Declaration of 1972 has the authority of a moral exhortation and nothing more. It is, for me, a cheering sign of sanity that Britain, though not even a signatory to the 1972 Declaration, has acquiesced — though often with ill grace — in many environmental directives from Brussels. The ill grace was not without provocation: the drafting of some of the directives was ham-fisted, not to say stupid; and Britain, having been the first European nation to despoil her environment, has learnt, better than any other European nation, how to repair the damage. So Britain had valuable experience to offer Europe. Has the offer been welcomed? On the whole, no. Nevertheless Britain has accepted the moral, if not legal, obligation to surrender some sovereignty over the control of her own air, water and land. Mr Haigh's book is a critical study of this unrecorded and remarkable influence of the Community on British policy.

If Mr Haigh has a fault, it is an excess of modesty. He calls his volume a "handbook" accompanied by an "essay". It is in fact a penetrating and perceptive analysis of the evolution of an environmental policy for Europe and Britain's response to it; written with scrupulous regard for accuracy and fairness; critical in places but always courteously so; offering opinions of his own which are clearly the result of very careful assessment of a mass of material: a book of outstanding quality. The only justification for calling it a handbook is the systematic way in which the case-studies of over thirty Commission documents are treated; for each one there are the formal particulars, a summary of the content, and an account of how it developed and its effect on practice in the United Kingdom.

In his introductory essay, Mr Haigh describes the historical and administrative

framework into which Community law has to be set. Immediately the problems appear. It is British policy to delegate responsibility and discretion to local authorities; to impose a blanket-regulation from Brussels upon a county council or a regional water authority is to weaken this cherished tradition. It is British policy, too, to be deliberately imprecise over some matters (was it not Churchill who said that we never create a distinction without blurring it!). For instance we are content in Britain to prescribe that our drinking water shall be "wholesome"; the European Council Directive of 15 July 1980 on the quality of water for human consumption specifies 63 parameters, from colour to coliform count, which have to be at acceptable levels. No wonder, when a stream of draft directives began to flow into Britain, there was a conflict between the often complacent pragmatism of the British and the often arrogant rigidity of the Europeans across the Channel. The most serious encounter was over the protection of what directives call "the aquatic environment". Do you fix an upper limit to the level of pollutants that can be discharged into the aquatic environment, from a pulp mill or a titanium dioxide works, to be the same from Scotland to Greece? Or do you take into account that the capacity of the receiving water to dilute and disperse the pollutants is greater in the Atlantic Ocean than it is 300 miles up the Rhine; and that it is the quality of the receiving water that should be the criterion for control of pollution?

Mr Haigh, in his case-studies, deals with this and a dozen similar conflicts with sympathy for both sides. On one hand many of the draft directives have been shoddily prepared, with totally inadequate scientific backing — in some instances not even consistent with the scientific advice the Commission itself sought. They deserved, and got, scathing criticism from the House of Lords scrutiny committee set up to deal with directives. On the other hand the British government has often adopted attitudes as pedantic as anything that has come from Brussels; it has on occasion been querulously defensive, and sometimes (for example in citing, in its defence, provisions in the Control of Pollution Act that had not been implemented) downright disingenuous. These and other faults on both sides are dealt with fairly and impartially, but Mr Haigh disciplines himself severely to keep within his self-imposed terms of reference, which are to examine the influence the Community has had on environmental policy in the United Kingdom. He admits that it is hard to isolate the influence of the Community from other contemporary influences: the ten reports from the Royal Commission on Environmental Pollution, for example, and the pressures from environmental lobbies (to which, in my view, he gives too little weight). But he does make a case for some impact from

Brussels: the belated decision to set (rather than just waffle about) environmental quality objectives in rivers; the agreement to adopt mandatory air quality standards for sulphur dioxide and particulates; some features of the Wildlife and Countryside Act; and (a more dubious benefit) the substitution of control by regulation in place of voluntary agreements (which for detergents had been entirely successful).

The chapter on the British influence on the Community is brief, but that is not what the book is about. I'm sorry, however, that Mr Haigh did not make one point which would, if the Commission in Brussels would listen, greatly smooth the path of negotiation over directives. That is to demand that the Commission should publish regularly, from the mass of data it receives, comparable figures to show the different degrees of compliance among member states with these directives. From several sources one can see the trend in sulphur dioxide emissions in Britain over the past ten years; one can see also the changes in the mileage of rivers of different qualities; the levels of dust in the air; and so on. But where can one find, so easily accessible, data from any other member state in the Community? And how, without such baselines for environmental trends in each member state, can one devise an environmental strategy for Europe? The EEC has dismally failed to provide these comparative data. Summaries in the Environmental Action Programmes are worthless, for they have nothing to say about the implementation of the laws that look so good on paper.

Mr Stanley Johnson's book, like the official publications from the European Commission, contains a suave sanitized version of the environmental legislation, with scarcely a hint of the controversies and political scheming that have so often distorted its intentions. The book, despite its pretentious title, is (as Mr Johnson admits) "purely documentary", an assembly of texts, all of them already published. In places it goes into tedious detail, giving (for instance) the full names of 129 chemicals that could belong to the notorious "black list" of substances to be "eliminated" from the aquatic environment. It is useful to have in one volume a catalogue of the environmental directives; but such critical assessments as the book contains are as bland as those one finds in a mail-order catalogue. It is disappointing that the vice-chairman of the European Parliament's Committee on Environment can offer nothing more than this. In contrast, Mr Haigh's book is a solid contribution to the debate on an environmental strategy for Europe. □

Lord Ashby serves on the House of Lords sub-committee which scrutinizes draft directives on environmental issues from the European Commission. He was chairman of the Royal Commission on Environmental Pollution from 1970 to 1973.

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The shooter and the shot

Edward Abraham

Alexander Fleming: The Man and The Myth.

By Gwyn Macfarlane.

Chatto & Windus/Harvard University Press: 1984. Pp.304. £12.50, \$20.

GWYN Macfarlane prefaced his biography of Lord Florey with an aphorism attributed to Voltaire: "We owe consideration to the living; to the dead we owe only the truth". He might have saved it for this following volume. But "what is truth" said Francis Bacon's jesting Pilate. The fluent prose of *Alexander Fleming: The Man and The Myth*, a book which provides a definitive assessment of the role of Sir Alexander Fleming in the story of penicillin, should persuade readers to stay for the author's answer.

In the 1940s there was world-wide gratitude for penicillin. Fleming found that fame had been thrust upon him and that he alone had become associated in the public mind with the name he gave to an active "mould broth filtrate". But his discovery had been made in 1928. André Maurois and others have presented their views on the eclipse of penicillin during the intervening years. Gwyn Macfarlane has now written the most detailed of all the biographies and has taken pains to consult primary sources. As one who has made distinguished contributions to medical research but has no personal place in this story, his judgement deserves respect.

Fleming's Scottish background and the events which led him from an Ayrshire farm to St Mary's Hospital are the subjects of early chapters. The farm held no future for him, as a younger son, and he took the road to London, like many Scots before him. Living with a brother, he attended the Regent Street Polytechnic and then became a junior clerk in the American Line.

It was an unexpected legacy of £250 that enabled Fleming to study medicine, and he apparently chose St Mary's because he had once played water-polo against the hospital team. Later, another seeming irrelevancy — that he was a fine shot — deflected his thoughts of becoming a surgeon. To keep him in St Mary's rifle team a colleague persuaded Sir Almroth Wright to take him as a part-time research assistant. By this time we see him as a modest man who was remarkably good in examinations, and enjoyed games and company, but who was so lacking in conversation that his blue eyes were said to be sometimes immobilized in a basilisk stare.

The book contains an amusing sketch of Almroth Wright, a formidable intellectual, full of conviction that his mental powers would reveal the solutions of medical problems, on whom Bernard Shaw

modelled Sir Colenso Ridgeon in *The Doctor's Dilemma*. He had produced a vaccine that offered protection against typhoid fever and was persuaded that vaccines would cope with bacterial infections in general by stimulating phagocytosis. Fleming, who never liked to stray far from experimental facts, was as different from Wright as Florey was from Chain, but he became Wright's disciple in a newly created Inoculation Department which financed itself by the sale of vaccines.

In 1921, Fleming made an unexpected observation. While suffering from a cold, he isolated, apparently from his nasal mucus, a rare coccus which he then showed was lysed by nasal mucus and thus discovered lysozyme. Macfarlane wonders why the mucus was tested against an organism that had survived in its presence and suggests that the experiment might be placed in the random category condemned by Wright as a sin against the Holy Ghost. However that may be, Fleming regarded his work on lysozyme as his best contribution to bacteriology.

His second major discovery, in 1928, was at least as extraordinary as the first. He was not looking for an antibacterial substance but for staphylococcal variants because he had been asked to write an article on *Staphylococcus*. A seeded plate he had put aside was later found to be contaminated with a *Penicillium* and around the fungus bacterial colonies were apparently undergoing lysis. But since penicillin lyses only growing staphylococci and not fully grown colonies, how did this come about? Macfarlane accepts the convincing explanation given by Ronald Hare in *The Birth of Penicillin*: cool weather allowed the fungus to grow first and produce penicillin; it then became warmer, and the bacteria grew and underwent lysis.

Fleming deserved praise and gratitude for his acute observation and for the curiosity which prevented him from discarding an unexpected contaminant, as others might have done. He showed that his culture filtrate had selective activity against bacteria and that it was not toxic to leukocytes and a rabbit. He thought at first that it might be used for the local treatment of septic wounds, in which other anti-septics had been worse than useless because they killed leukocytes before bacteria. But when "there was no miraculous success" he was quickly discouraged and wrote in 1940 that "the trouble of making it seemed not worthwhile". In his paper on cultures of a *Penicillium* in 1929 he made "special reference to their use in the isolation of *B. influenzae*", which he had studied during the influenza pandemic of 1918, and presumably had in mind the preparation of a vaccine.

In 1936, when Colebrook was demonstrating at St Mary's the ability of prontosil to cure dangerous streptococcal diseases, Fleming carried out experiments in mice and rabbits to determine whether a

combination of vaccine and sulphonamide treatment would be beneficial, but he showed no renewed interest in penicillin. The evidence is overwhelming for the conclusion that neither he nor anyone else at that time envisaged that penicillin would be a systemic therapeutic agent. Perhaps, as Macfarlane suggests, Fleming's attitude was conditioned by a finding that penicillin



Fleming in caricature, as "Private 606". A cartoon by Ronald Gray, 1911.

disappeared rapidly from the blood and his belief that it was inactivated by serum.

Penicillin was not forgotten, however, when Howard Florey and Ernst Chain of the Sir William Dunn School of Pathology decided to make an academic study of the antimicrobial substances known to be produced by microorganisms. The decision was a consequence of Florey's earlier interest in lysozyme and the urgent need to obtain money for research. Its outcome, made possible by the efforts of a small group of people under the constraints of war, was Florey's demonstration in 1940 that even very impure penicillin could protect mice from otherwise lethal systemic

infections with streptococci and staphylococci, and the finding in 1941 that it could save patients from infections that would previously have been regarded as fatal.

The results obtained at Oxford transformed penicillin from a biological curiosity into a substance with great potential in medicine. A letter from Almroth Wright to *The Times*, in which he placed a laurel wreath on Fleming's brow, was followed by a flood of misleading publicity. Gwyn Macfarlane attempts to throw light on how it happened that Fleming was credited with a vision he did not have and even with work he had not done, while the discovery at Oxford, if mentioned at all, was presented as a minor development. It is clear that Florey had no wish for notoriety when so little penicillin was available and turned journalists away. As to what occurred at St Mary's the author can only surmise, but he points out that the Medical School had a history of poverty, and consequently of fund-raising, and that its Dean, Lord Moran, numbered Lord Beaverbrook (no stranger to publicity) among his influential friends.

Fleming himself made no exaggerated claims, although he acquiesced in what was happening and occasionally insinuated that the short-comings of others were responsible for his failure to exploit his discovery. Towards the end of the book we have an entertaining account of the effect of his rise to fame on his later life. Innumerable invitations, often involving long travel and coupled with scientific and social programmes that would have daunted many a younger man, were accepted without hesitation. But he received the praises of the crowds with becoming modesty and certainly never succumbed to *folie de grandeur*.

The main reason for concern about the Fleming myth was the possibility that it would permanently falsify the history of a dramatic medical advance. It had little influence on the judgement of the scientific establishment. Although the first clinical trial made it likely that penicillin's contribution to medicine would be immense, the work that had brought this about had made no comparable contribution to science. Florey wrote "The almost miraculous properties of penicillin should not blind us to the fact that the work carried out at St Mary's Hospital, London, and at Oxford introduced no new chemical or biological principles. The results, however, were new and the effects on medicine widespread". No one could have foreseen, in 1941, the chemical and biological developments which were to give the β -lactam antibiotics a scientific interest for a further forty years and continue to do so today. But this story lies outside the scope of Gwyn Macfarlane's book. □

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Arms across the waves

Laurence Martin

The Independent Nuclear State: The United States, Britain and the Military Atom.

By John Simpson.

St Martin's Press, New York/Macmillan Press, London: 1984. Pp.340. \$30, £25.

A KINDLY angel must have supervised the gestation of Dr Simpson's enterprising book, for he begins by explaining that he intended to write on a different subject altogether and that subsequent changes of plan have greatly delayed its completion. The result is that the book emerges at a most timely moment in both the politics and the historiography of British nuclear forces: politically because of the current and continuing debate over the British acquisition of *Trident II*, and historiographically because a great deal of hitherto highly secret information is beginning to appear in the United States. Indeed it is one of the few and unavoidable limitations of this book that already it needs updating by reference to recent disclosures. So much more closed is the British defence establishment than the American, however, that this new information affects the context rather than the substance of the British story, and Dr Simpson's heavily documented account is likely to remain standard and invaluable for some years to come.

Scientifically competent readers will doubtless take particular interest in the author's effort to put precise numbers on the scale of British military nuclear production, by means that he himself admits to be crude and disputable. For those with a more general concern for the strategic and political implications of the British nuclear force, it is instructive to note that the current generally accepted "force loading" of the British submarine strategic force of about 200 warheads, is exactly the goal set in 1948 for achievement in 1960. This may say something about the stability of British conceptions of an adequate "assured destruction" capability, especially if we assume some rough correlation between the off-station factor in the submarine force and the likely attrition of its airborne predecessor. Whereas, however, the 1948 projection was conceived to be about half the American capability, today's British force is eclipsed in scale by that of the United States. The record of the British nuclear effort is, indeed, one of being steadily overtaken, though running a very game race. In 1941 Britain was probably the leader; by the time its national programme approached the point of acquisition of weapons, a decade later, Britain was already trailing the Soviet Union and about to become the world's first "Nth nuclear power".

Dr Simpson's book, like Professor Margaret Gowing's official histories of the very early years, affords intriguing glimpses of mixed and often conflicting reasoning that has led successive British governments of both political parties to persist in a game in which the odds are uneven but in which not even the outsiders are negligible. The game is not made easier by continual changes in the rules. At the beginning the problem was to get the bomb; by the 1960s the trick was to deliver it. At the outset having the bomb was thought to be more important than knowing what it was for. In 1947 the Foreign Secretary, Ernest Bevin, was content merely to argue that Britain "could not afford to acquiesce in an American monopoly in this new development". When, in 1948, the RAF specified a force capable of attacking 59 Soviet cities — even though many members of the Labour Cabinet would not accept that the Soviet Union was an enemy, a scruple the Berlin blockade and Czech coup were to remove — policy was still concerned with tactics rather than strategy. Only in 1952, when the British Chiefs of Staff devised and later sold to Churchill when restored to power a "grand strategy" based on deterrence by nuclear retaliation, could it be said that the expensive and secret weapon programme was harnessed to a strategic theory — albeit a debatable one.

It has long been known that the incoming Eisenhower Administration drew some support from the British strategic theory in evolving its own doctrine of Massive Retaliation. The whole British story is, of course, intimately bound up with the United States. The relationship was and is a complex one, and the motives, principles and prejudices of so many different layers of the pluralistic American machine — politicians, military and scientists — made it difficult for the United States to pursue a consistent policy.

What the British needed from the United States — help in reducing costs — was rather simpler, and they were not without levers: among them their undoubted skill and know-how, even if those of the junior partner, the goodwill of past co-operation, and such legal holds on the United States as the Quebec agreement of 1942 requiring British consent for American use of nuclear weapons and agreed rights to a share in scarce uranium supplies from the Congo. Less tangible but nonetheless effective was the power Britain paradoxically enjoyed by being the weaker partner in an enterprise — the containment of the Soviet Union — of great importance to the United States. Merely by implication — often genuinely without any intention of doing so — Britain could threaten to divert its resources from supplying the conventional strength NATO needed, could show signs of paying a political price, perhaps even a price in nuclear co-operation, to win a French welcome to the European Community, or could obstruct an arms control initiative dear to America.

In the case of arms control, as in several other aspects of policy, Dr Simpson's detailed account of British policy makes clear how often things were not what they seemed, how often apparent virtue masked more selfish motives, and how good causes produced unanticipated effects. This was particularly clear in the 1950s with initiatives for "Atoms for Peace", for a test ban, and for a cut-off of fissile material production. As keen as the Eisenhower Administration was on impeding the Soviet erosion of American nuclear superiority and on discouraging the French and Chinese nuclear programmes, the British were still on the wrong side of the line so far as actual achievement of their own stockpile was concerned, particularly of thermonuclear weapons. They were able to use their obstructive potential to win help in accelerating their programme through the 1958 amendments to the MacMahon Act. As a precaution Britain had also accelerated its plutonium output, however, and once American assistance led to more economical warhead designs, was able to barter plutonium for further assistance. All quite useful, perhaps, but not what was originally intended and rather remote from the issues with which political debate in either country was ostensibly concerned.

A better known paradox of the British nuclear relationship with the United States is illuminated by Dr Simpson's characterization of the roles played by Britain's two leading political parties. As Ernest Bevin's remark quoted earlier reminds us, the Labour Party, presumably because of a latent suspicion of the United States, was not only the founder of the independent British nuclear programme, but the more insistent that it should be independent. The first British tests were conducted in Australia rather than, as might have been possible and cheaper, in the United States, chiefly because Clement Attlee was unwilling to become dependent on the Americans. Churchill, by contrast, was much more inclined to see the nuclear programme as a tool in strengthening Anglo-American relations, even at the price of some loss of independence. It was Macmillan who based British nuclear power on an American missile but Labour Governments under Harold Wilson and James Callaghan which

secretly completed the new re-entry vehicle *Chevaline* and reacted to a rising tide of American anti-proliferationism, especially under President Carter, by establishing a national source of tritium and reopening stages of the British enrichment plant. Once President Reagan changed the rhetoric, it was the subsequent Thatcher Government that slowed down this process and purchased yet another American missile.

In the last and inevitably most speculative part of his book, Dr Simpson considers the future of this trans-Atlantic nuclear relationship and of the British force within it. Reluctantly he comes to the conclusion that Britain could not readily become a non-nuclear power even if it wanted to do so; it is too impregnated with knowledge and capability. This observation constitutes yet another recognition of how elusive the distinction between nuclear and non-nuclear powers becomes as understanding of nuclear engineering proliferates. Nuclear weapons play their part chiefly as latent factors in political relations. Hence the importance attached to the status of Israel and India as virtual nuclear powers or to Argentina and Pakistan as nearly-nuclear powers. Somewhat the same relativism is appropriate in contemplating the pervading question raised by Dr Simpson's book: just how independent is the British deterrent? The brief reply is that there is no simple answer to such a question; most of the time derivative weapons, like potential weapons and suspected weapons, can all play some part in the political balances.

Nevertheless the state of Anglo-American nuclear relations is a major influence on the tone of the alliance, and one reason Dr Simpson's book is timely is that several current trends could radically alter that relationship in the next few years. In Britain, the chief source of instability lies in the Labour Party's move outside the bipartisan consensus that has prevailed since the 1940s. In the United States, if the mood represented by Dr Henry Kissinger's recent demand that the Europeans should show greater self-reliance in defence gains much ground, it must inevitably become entangled with Mr Robert McNamara's parallel insistence that the United States offer less by way of nuclear guarantees to Europe. The relatively relaxed British attitude to the question of dependency or independence has flourished under the shade of a sturdy American nuclear umbrella. It is too early to say what the outcome would be if the web of mutual Anglo-American understanding in nuclear matters began to unravel. The story told by Dr Simpson does suggest one firm prediction, however, and that is that the result is highly unlikely to be exactly what anyone intended. □

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Binary weapons: the monster is loose

John Erickson

No Fire No Thunder: The Threat of Chemical and Biological Weapons.

By Seán Murphy, Alastair Hay and Steven Rose.

Pluto Press: 1984. Pp.145. Pbk £3.95.

MANY years ago we bravely faced the "bomber gap". Latterly we have been strenuously persuaded of the "missile gap" in its various configurations, not to mention the attendant "window of vulnerability" — the metaphors tend to become a little mixed — but we are back again with what is currently advertised as the "gas gap". The deterrent, or one component of it, is again threatened, or so Richard L. Wagner, assistant to the US Secretary of Defence, asserts. "The United States currently lacks a deterrent to a Soviet chemical weapons attack in Europe", since there is no counterpart to match Soviet capability to lay down a persistent gas screen beyond the 10 kilometre artillery range.

Soviet forces, equipped with binary weapons and "14 or 15 chemical weapons capable of being delivered at long ranges", can deliver persistent agents deep within NATO's rear, well beyond artillery range, engulfing logistics, supply centres, airfields, and command and control links. At such ranges NATO forces must fight "buttoned up", encumbered with protective gear, while Soviet rear areas would be virtually immune: air delivery of chemical agents by NATO at present involves pilots flying what amounts to suicide missions, coming in low and on a predictable course, only to deliver antiquated munitions as a spray which disperses all too quickly. Hence the "gas gap", and weapons such as BIGEYE (a spray bomb for F-111 aircraft) as well as plans to develop some 15 types of munitions in the binary role.

The subject of chemical and biological warfare (CBW), while having its own arcane vocabulary, also exudes singular repulsiveness. "Binary weapons" sound almost clinically clean, shut away from this house of horrors, but the monster is loose, striking most recently in the Iran-Iraq war where mustard and nerve gases have been used. This alone would give *No Fire No Thunder* not only great timeliness but also added value as a guide to this particular type of warfare, BIGEYE included as well as those reports from South-east Asia and Afghanistan. In the latter context, operations in Afghanistan, the reader can usefully turn to an article by Dr E. M. Spiers, "Gas and the North-West Frontier", published in *The Journal of Strategic Studies* (December 1983), a review of British attitudes to gas and "frontier difficulties".

Whatever the wrangling over the use of

Journal reviews 1984

The next review supplement to appear in *Nature* will be the New Journals Review, on 27 September. Criteria for journals to be considered for review are:

(i) the first number appeared, or the journal was re-titled, between June 1982 and May 1983 (these time limits allow for the publication of several issues of a journal, on which a reasonable judgement may be based);

(ii) the journal appears at least three times a year;

(iii) the main language used is English.

During May publishers will be requested to submit four issues of appropriate publications for review.

particular agents in Afghanistan and South-east Asia, chemical agents as such together with toxic trichothecenes — a form of “biochemical warfare” —, there can be no dispute about the onset of “chemical warfare” in the Iran–Iraq war. Both TABUN(GA), ethyl-*NN*-dimethylphosphoramidate cyanidate and mustard gas (dichloroethyl sulphide) have been used on the battlefield, all in a pattern strongly reminiscent of the use of chemical weapons by Italy in Ethiopia in 1935–1936, using this type of weapon against forces poorly equipped to neutralize their effects. That background, and indeed one much wider, bringing the story into the 1970s, is amply delineated by Chapter 2 of *No Fire No Thunder*: this account is especially useful for its careful classification of the various agents and their possible use. In short, the book is an excellent updating of the major six-volume work from the Stockholm International Peace Research Institute, *The Problem of Chemical and Biological Warfare*, first published in 1971.

To say that the whole subject is an emotive one is to make a massive understatement. The folk memories of the First World War, and of the release of 168 tons of chlorine by the Germans at Ypres in April 1915, have not faded. And during the Vietnam War, American public opinion was outraged at the use of emetic gas which caused enemy soldiers to vomit on the battlefield, part of public revulsion at weapons which kill “slowly”. The authors of *No Fire No Thunder* made excellent use of such historical examples to emphasize the “cynicism” of the wording of CW agreements — the Germans did not use *projectiles* to disseminate liquid chlorine — and the implications of a new arms race almost hidden under such euphemisms as “binary weapons”, not to mention a propaganda war of words designed to justify chemical weapons rearmament.

Though cynicism may be admitted in the drafting of agreements, deftly designed to provide loopholes, Dr Nicholas Sims has also underlined the significance of these niceties in his paper “Mycotoxins and Arms Control” (ADIU Report, December 1981) on the applicability of the Geneva Protocol of 1925 and the 1972 Convention on Biological and Toxin Weapons. This is not mere legerdemain but an issue of the greatest importance, one somewhat glossed over by the authors in their discussion of “yellow rain” in Chapter 4: it is perhaps a most unfortunate turn of phrase to insist on “healthy scepticism” about “yellow rain” when the whole context is decidedly unhealthy.

Meanwhile, the entire question of CW arms control has been raised anew with President Reagan’s latest proposals for banning the production, possession *and* use of chemical weapons, coupled as it is with a call for American investment in its own “limited retaliatory capability” in chemical weapons. With respect to that key issue, *verification*, Soviet officials have

already indicated willingness to open “declared” sites to inspection but refuse any comprehensive “right to look”.

Earlier talks in 1976–1979 between the superpowers founded on verification, a factor which may well prevent any global agreement in the future. Not all is lost, however, if we pursue Professor G.K. Vachon’s suggestion, made in *Survival*, that regional arrangements might be made for curbing CW, much on the lines of the Treaty of Tlatelolco banning possession and use of nuclear weapons in Latin America. In a sense, the industrialized nations have tended to regard the 1925 Protocol as a “no first use” undertaking, even though it is tacit; but the authors of *No Fire No Thunder*, in a chilling chapter, point out the utility of CBW in military situations. It is almost as if two escalatory arms races are fusing, one technologically highly advanced, the other in basic CW capabilities.

Though CB weapons are sometimes labelled as agents of “mass destruction”, this may be something of a misnomer, a point made with great precision in Chapter 5 of the book, on CBW and military

scenarios. Chemical weapons were used “strategically” in both the Sino-Japanese war and in Vietnam: Japanese interest in bacteriological warfare was quite purposeful, if one looks at a lecture delivered by Dr Enryo Hojo, *Über den Bakterienkrieg*, delivered at the Military Medical Academy in Berlin in 1941 (see US National Archives Microcopy T-82 Roll 90/246588–629) and subsequent evidence from the experiments in the Manchurian prison camps. *No Fire No Thunder* examines in some detail the operational scenarios involving quick-acting anti-personnel chemical weapons, the “mix” of conventional and chemical weapons, persistent agents and nerve gases — both rapidly clearing and long lasting. It is certainly an apt description to label these “search and denial weapons”: they are area weapons, they are undeniably “search weapons” (engaging both hard targets and dispersed forces), they afford considerable degrees of flexibility for a commander and they can inflict high casualty rates, particularly when used in surprise attack.

There is, however, the factor of unpredictability, whatever the precision of the planning. A recent computer study has

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REASONS

LUP/THP031601-03/16/84-AHVAZ, IRAN: A United Nations fact-finding delegation member kneels 3/14 to make photos of an Iraqi chemical bomb that failed to explode during an air raid in the southern Iran–Iraq border. The delegation arrived 3/13 and went to the contaminated fronts 3/14. UPI cs/irna

demonstrated that in any European conflict, with 1,000 tons of nerve gas used each day by both sides, civilian casualties would be counted in millions and the ratio of civilian to military casualties would be 20:1. While biological weapons are generally discounted for use on the battlefield — nerve gases act much more quickly — the authors of *No Fire No Thunder* do not ignore the "social repercussions" of CBW warfare, including the overwhelming of medical services and the breakdown of public order, not to mention the appalling consequences of the use of biological weapons in sabotage actions. I do not regard this as scare talk: consider the death, havoc and tribulations brought about with the deliberate random poisoning of a patent medicine in the United States, a small instance of what might come to pass.

If this were not enough, Chapter 8 outlines further developments in CB weapons, with discussion of the military exploitation of genetic engineering, bringing with it the possibility of "rampant pathogens and large-scale production of both known and new toxins". According to the authors, the search is on for "undercover tactical agents" specifically designed to debilitate the opposition. Nor does the work on chemical agents stop, with US binary munitions including a new agent crossed between Sarin and VX, "modified soman" (EA5774), and growing interest in civilian control agents.

The authors conclude, not implausibly, that both the United States and Soviet Union envisage operations in Europe which will be chemical as well as nuclear, though rational argument would suggest that no appreciable strategic or tactical gain can accrue from increasing CW arsenals. Yet the burden of Chapter 5 — on military scenarios — is that there is appreciable operational advantage to be gained from CW and serious potential in BW for sabotage and disruption. The last chapter takes the form of an impassioned appeal for chemical disarmament, for a "CW-free Europe" propounded by a pan-European movement: with Britain "a nuclear and chemically disarmed country", the authors go on to admit a need to consider the defence of the *population* against any chemical attack. I should have thought that might be considered even now, though politically it is ruled out if only because it raises the whole question of population protection, as opposed to shelter for select élites.

Meanwhile this timely, coherent and highly informative book should receive very wide attention: it is not comfortable reading but it is highly urgent reading, even for those who might think themselves informed on the subject. □

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Radiating sense

K.V. Ettinger and
J.E. Rimmington

Nuclear Radiation: Risks and Benefits.

By Edward Pochin.

Clarendon: 1983. Pp.197. £17.50, \$32.50.

... The B vocabulary consisted of words which had been deliberately constructed for political purposes, that is to say, which not only had in every case a political implication, but were intended to impose a desirable mental attitude. ... (George Orwell, *Nineteen Eighty-Four*).

THE complete edition of *Newspeak B Vocabulary* is not available through the book trade and we are not certain whether the expression "radiation protection" is a part of it. But whatever the gestation of this term, it served perfectly well to calm the minds of Project Manhattan workers, who, as we know nowadays, were on many occasions exposed to doses of radiation which would be unacceptable today.

Edward Pochin's *Nuclear Radiation: Risks and Benefits* serves as a reminder that a large part of radiation protection is just monitoring doses of radiation received by individual radiation workers, and that "protection" is afforded by the legislative process which itself is in part a function of public sensitivity on the matter. So that the reader may arrive at an informed comparison between risks and benefits of ionizing radiations (not only nuclear, as the title implies), the author gives a detailed exposition of the techniques of radiation measurement as well as an account of the amounts of radiation which we receive from natural and man-made sources. And so that the deleterious effects of radiation are understood, there is a good review of the relevant parts of radiobiology. The counterbalancing of risks and benefits is not discussed in quantifiable terms, however, simply because such analysis is not available as yet; after all "the quality of life" is not easily reduced to numbers.

Instead, in his final chapter Pochin provides a careful comparison between risks (expressed in number of deaths per

Nuclear power

Oxford University Press have issued a major reference work in three volumes, *Nuclear Power Technology: The State of the Industry*, which (according to the publisher) "will provide the scientist and layman alike with a comprehensive and up-to-date reference on all aspects of nuclear power".

Editor of the work is Walter Marshall, Chairman of the Central Electricity Generating Board, and the contributors are all specialists drawn from the industry itself. Titles of the individual volumes are: *Reactor Technology*, *Fuel Cycle* and *Nuclear Radiation*. Price is £35, \$65 per volume.

100,000 per year) for various occupations and for workers exposed to cancer-causing agents, and also gives the general number of fatalities due to accidents. This comparison indicates that it is a valuable exercise to analyse avoidable risks in many industries and, as a corollary, to get rid of those technologies and agents which needlessly contribute to the misery, high death rate and sickness of people exposed to them. Again, however, it is extraordinarily difficult to weigh the risks against the benefits of these factors in precise terms since we are often dealing with a situation in which industry benefits financially from the technologies it uses — the risks are borne by the employees personally and by the state fiscally, but how do we compare individual risks with community benefits or vice versa?

Be this as it may, and despite the fact that Pochin's tables indicate that radiation hazards are not the top priority if resources are limited, for many the conclusion to be drawn from the book is that positive action is needed: a determined effort to reduce and even eliminate the use of ionizing radiation in all circumstances in which it can be replaced by other agents. Recently developed analytical techniques, both chemical and physical, offer the possibility of replacing radioactive tracers by stable compounds. Many of the gauges used in industry for measurement of thickness, moisture content and so on can be replaced by instruments based on other techniques, and it is worthwhile examining alternatives to industrial radiography. A similar approach has already been taken in the field of medical applications of radiation and radioisotopes. The use of nuclear magnetic resonance for tissue imaging is making fast progress and the population-averaged radiation doses from medical radiology, which according to Pochin exceed those from radiotherapy, should be gradually reduced to the unavoidable minimum. Obviously, the nuclear industry, and particularly the nuclear power industry, are the cynosure of the public eye in this respect, and the subjects of a broader debate.

The book is well and smoothly written, with a sense of wry humour, though it sadly lacks extra drawings, photographs and graphs which could have made the going so much easier. Those illustrations which are included seem to be the end result of some random selection. Nonetheless the book can be certainly recommended to those who are concerned with the effects of ionizing radiation, whether professionals or laymen. They will acquire an excellent source of information, impartially presented. But it will not serve everybody equally well. After all, it was Winston Smith who said: "Ignorance is strength". □

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Holocene alluviation and hydrology in the upper Thames basin

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A sequence of changing conditions for flooding and alluviation in the upper Thames valley during the Holocene has been identified and provisionally dated by the investigation of archaeological sites interstratified with alluvium. Archaeological survey suggests that the changes can be related to clearance and agricultural activity in the catchment area.

MANY river valley bottoms in lowland Britain are characterized by Pleistocene terraces of gravels or sands into which are incised floodplains covered with Holocene overbank deposits of clays, silts and loams. Such alluvial deposits are particularly difficult to date unless contemporaneous organic remains are available for radiocarbon determinations.

Although the potential contribution of archaeology in elucidating the palaeohydrology of floodplains has long been recognized^{1,2}, it has seldom been applied systematically. However, it is becoming evident that archaeological sites interstratified with alluvium frequently occur in some British river valleys, and the need for a closer relationship between archaeology and studies in Holocene palaeohydrology has recently been stressed³. Archaeological remains found beneath alluvium include settlement sites with the remains of houses and spreads of occupation debris, religious monuments such as burial mounds and cursuses, other ditch systems and trackways⁴. These sites can be dated by radiocarbon determinations on organic remains and standard archaeological methods using artefact and site typologies. The usefulness of archaeological dating should not be underestimated: a Bronze Age barrow cannot be redeposited while dates based on good artefactual evidence are sometimes as accurate as those from radiocarbon determinations.

Apart from the important role of archaeology in the dating and interpretation of floodplain deposits themselves, it is one of the few means of assessing directly the impact of human activity on prehistoric hydrological systems³.

Despite this, archaeological survey of drainage basins has not become a standard part of palaeohydrological studies.

Data collection

Several lines of evidence were used from various archaeological sites excavated by the Oxford Archaeological Unit. They include alluvial sedimentology, soil development, the degree of organic preservation by waterlogging and the ecology of Mollusca in both natural and archaeological deposits. The value of the different types of data varies between sites, depending on preservation, topography and the range of archaeological deposits. As a result, only some of the sites provide positive evidence for any particular part of the sequence, while the others either present comparable stratigraphy without the dating evidence, or lack the relevant deposits but are not otherwise contradictory.

The location of the sites examined by us and the general topography of the upper Thames basin are shown in Fig. 1. Site 1 is on the lower Windrush floodplain, the others are on the Thames floodplain. Sites 2, 4, 6a, 8 and 9 are on the main body of the floodplain, but the top of the underlying floodplain gravel varies in height above the river level and these sites have different thicknesses of alluvium. Sites 1, 5, 6b and 7 are on the

edge of the first gravel terrace or high areas of the floodplain and not all of them have a continuous alluvial covering. Site 3 is in the top of a silted river channel. Stratigraphical and other data for the sites are presented in Figs 2, 3 and 4. Figures 2 and 3 give slightly simplified composite sections, and Fig. 4 shows part of the Drayton deposits as observed. Radiocarbon determinations are quoted in uncalibrated years before present (1950), to one standard deviation, using the 5,570-yr half life. Some additional information is relevant for the following sites. **Site 3:** The Bronze Age occupation horizon produced a molluscan fauna characteristic of relatively dry grassland (95% terrestrial species with high proportions of *Vallonia excentrica* and *Pupilla muscorum*). *V. excentrica* and *P. muscorum* were virtually absent from the alluvium immediately covering this horizon, which contained up to 80% aquatic molluscs.

Site 5: The bottoms of two Bronze Age barrow ditches were filled with yellow-brown, almost ungleysed clays and loams with poor organic preservation. Three Iron Age house circle ditches of similar depth contained grey gleyed clays and loams with waterlogged organic remains at the bottom. One ditch of each period is illustrated.

Site 6a: Flooding contemporary with the Iron Age occupation was indicated by riverine aquatic molluscs such as *Bithynia tentaculata*, with their periostraca intact, in small, isolated, peat-filled ditches, which would have been too small for these molluscs to have survived and bred in them. After abandonment, the water table rose to at least the level of the occupation surface, resulting in the survival of organic remains.

Site 6b: Peat containing late Roman pottery accumulated over features datable to AD 250–400 on the edge of the first gravel terrace, 0.45 m higher than the Iron Age ground surface at Site 6a on the floodplain. At least some alluvium must have been present on the floodplain for this to have occurred.

Site 8: The alluvial clay covering the reedswamp deposit is interpreted by the excavator as redeposited to form a Saxon causeway⁵.

In addition to these sites an exposure has been described at SP360084, where *in situ* alder roots in the floodplain gravels of the Windrush beneath alluvium were dated $2,660 \pm 85$ BP (I-9337)⁶. Unfortunately, its value is reduced because it is possible that the roots grew through some or all of the alluvium, but were only preserved below the water table.

The Holocene sequence

In the late Devensian, minor and rapidly shifting channels reworked part of the first Thames terrace and lowered it to create the undulating gravel surface beneath the modern floodplain^{7,8}. There was no significant Holocene reworking of the floodplain gravels⁷ which, together with evidence of a major late Devensian channel at Farmoor^{9,10}, suggests that river flow

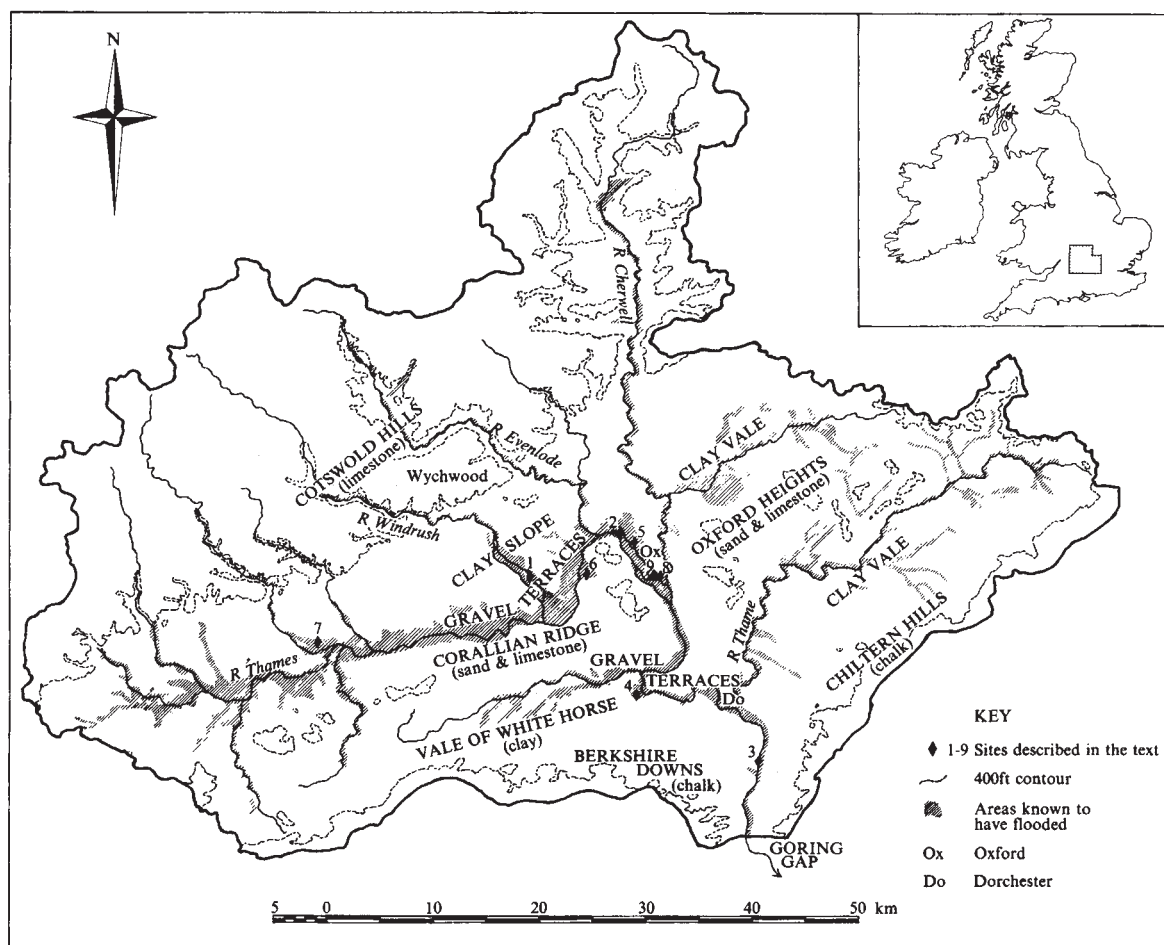


Fig. 1 The upper Thames basin (information on flooding from Thames Water Authority).

became restricted to channels eroded to their greatest size before or during the early Holocene. Excavations and air photography indicate a more complex pattern of channels in early post-glacial times than survives today, otherwise the channel system has remained relatively stable.

A study of channel development of the River Gipping in Suffolk has similarly shown channel movement in the late glacial, and channel stability throughout most of the Holocene¹¹. Channel instability was attributed to periods of high, short-lived, discharges caused by seasonal snow melt.

Except possibly for the lower Windrush, there are no extensive earlier Holocene organic backswamp deposits beneath the mineral sediments of floodplains in the upper Thames basin. However, fringing swamps existed in places along the Thames and it is possible that the early Iron Age reedswamp at Site 8 had a much earlier origin.

The relative contribution of alluvium, loess and weathering products of the gravel to the sediments stratified beneath prehistoric sites on the floodplain is uncertain, but all probably played a part. By the Neolithic, pedological processes seem to have predominated over alluvial accretion for much of the floodplain, and only a thin soil, not necessarily of alluvial origin, covered the gravel on some of these sites. The pre-Iron Age soil of Site 1 was certainly partly alluvial in origin, but a long period of earthworm activity had transported all the shells of aquatic Mollusca to the bottom of the profile, above which it was decalcified. Most of the pre-Iron Age soils are ungleyed and non-calcareous. At Site 3, the molluscan fauna was of relatively dry grassland, in contrast to the mixed wet grassland and aquatic assemblages characteristic of the later alluvium here and elsewhere. It is difficult to prove that flooding without alluviation was not taking place, but at Sites 2 and 4, where man-made dumps of limestone gravel sealing the pre-Iron Age surface of

the floodplain would have buffered any later phases of decalcification, shells of aquatic molluscs were absent.

The lack of preserved organic remains or much gleying in Neolithic and Bronze Age ditches, in contrast to later ones of similar depth, suggests at least a seasonally low water table on the floodplain.

Between the middle to late Bronze Age and the middle Iron Age, by which time good organic preservation and much gleying are evident in ditch fills, a rise in the water table of the floodplain took place. Sites 1 and 5 provide internal comparisons. Site 6 produced direct evidence that flooding was occurring by about 2,400–2,050 BP. It is likely that this represents the onset of regular seasonal inundation of much of the modern floodplain.

Alluvial clay, characterized by aquatic molluscs (where preserved), sealed prehistoric deposits at Sites 1, 2, 4, 5, 6 and 8. Nowhere was it observed stratified earlier than mid-Iron Age deposits but Sites 4 and 6 show that this alluviation was well under way in the Roman period. Its accretion may have begun in the late Iron Age. Organic preservation at Sites 1 and 6 suggests a continuing rise in water table after Iron Age occupation. Similar evidence at Site 4 shows that the Roman water table was much higher than it had been in the late Neolithic.

It is uncertain whether alluviation or flooding continued into the early Saxon period. A distinct upper layer of alluvium, coarser in texture and containing abundant molluscs, overlay the clay alluvium at Sites 4 (post-Roman) and 6a, and less definitely, at Sites 8 and 9 (AD 900–1200). Similar deposits were observed at Site 7 (post-late Roman) on the edge of the first gravel terrace and Site 1 (post-mid Saxon). These deposits may represent late Saxon and early medieval alluviation extending further than the earlier clay alluvium.

The depth of organic preservation in archaeological features shows that the water table on the floodplain remained high to

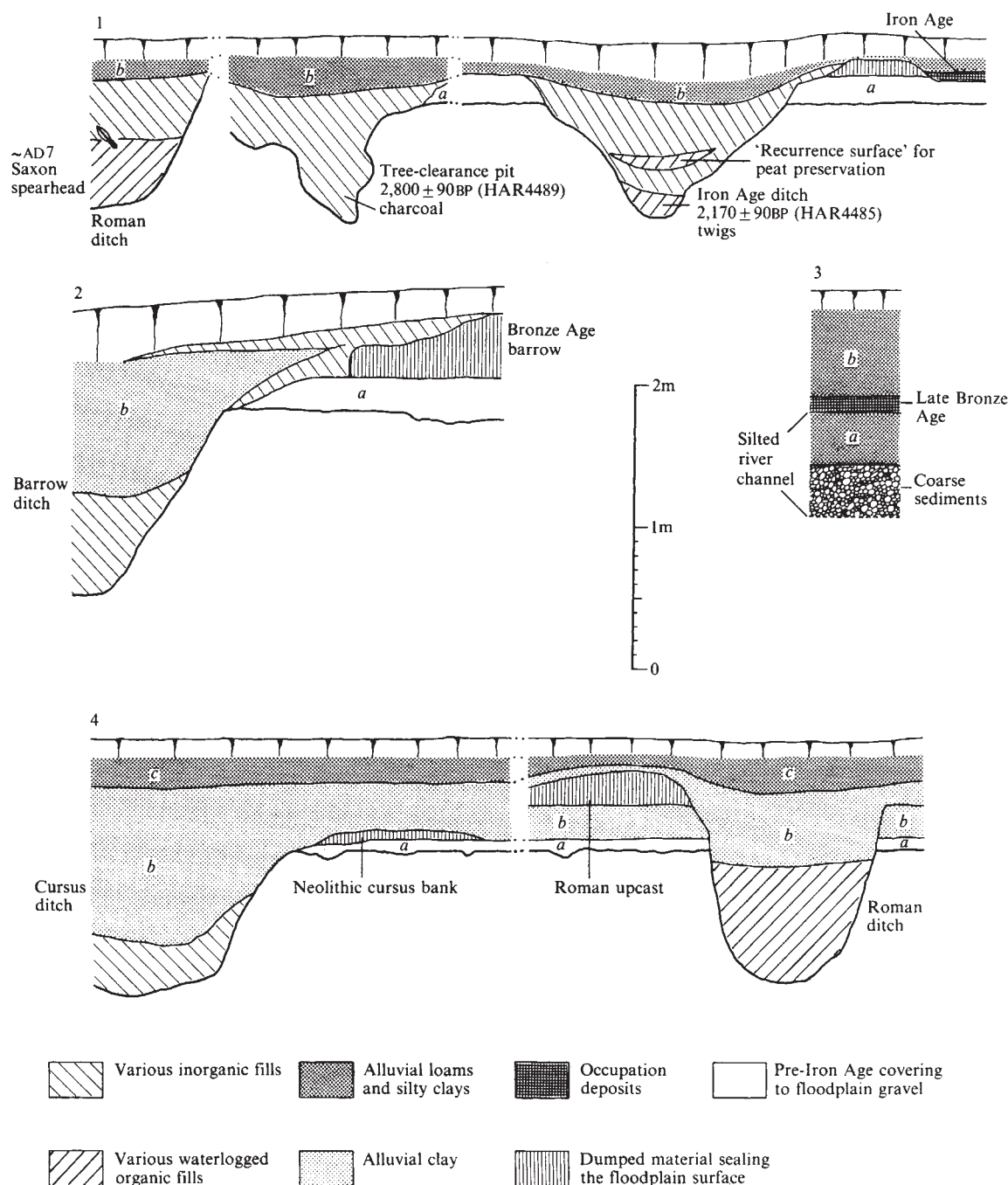


Fig. 2 Simplified composite sections of the alluvial exposures. Site 1, Mingie's Ditch (SP391059). *a*, Earthworm-sorted yellow-brown silty clay; *b*, non-worm-sorted mollusc-rich loam. Site 2, Kings Weir⁴² (SP476102). *a*, Red-brown silty loam; *b*, gleyed clay. Site 3, Wallingford (SU607882). *a*, *b*, Clayey to sandy loams, *a*, more clayey. Site 4, Drayton (SU490943). *a*, Yellow-brown sandy clay loam; *b*, gleyed clay; *c*, clay loam (see also Fig. 4).

the present day, and historical records show that seasonal flooding continued throughout the medieval and post-medieval periods¹². Alluviation, however, may have decreased from the late Middle Ages onwards: post-medieval objects commonly occur on the floodplain but seem confined to the modern 'A' horizon.

Possible causes of change

The Goring Gap provides a base level for the upper Thames, thus isolating the region from the effects of sea-level changes. Although the rise in water table of the Thames floodplain between the late Bronze Age and the middle Iron Age occurred at a time when it is considered the English climate was becoming cooler and/or wetter^{13,14}, this was also a period of agricultural expansion. The subsequent changes in hydrology do not corre-

late well with postulated changes in climate, but can again be related to differences in land use.

It is well established that man has considerable influence on hydrological and alluvial regimes. The replacement of woodland by grassland has the effect of raising groundwater levels, and increasing surface run-off and stream flow. Flow rates become more uneven, increasing the likelihood of flooding¹⁵. Many studies, some in temperate regions, have shown greatly increased sedimentation in lakes and other waterways following clearance of woodland, particularly on conversion to arable¹⁶⁻¹⁸. In south-west Britain the removal of grassland on hill slopes is estimated to have increased soil movement by ~400 times¹⁹. Surface rainwater flow and the consequent erosion are readily observable on ploughed slopes in the region at present. It should also be expected that technical changes in drainage, cultivation

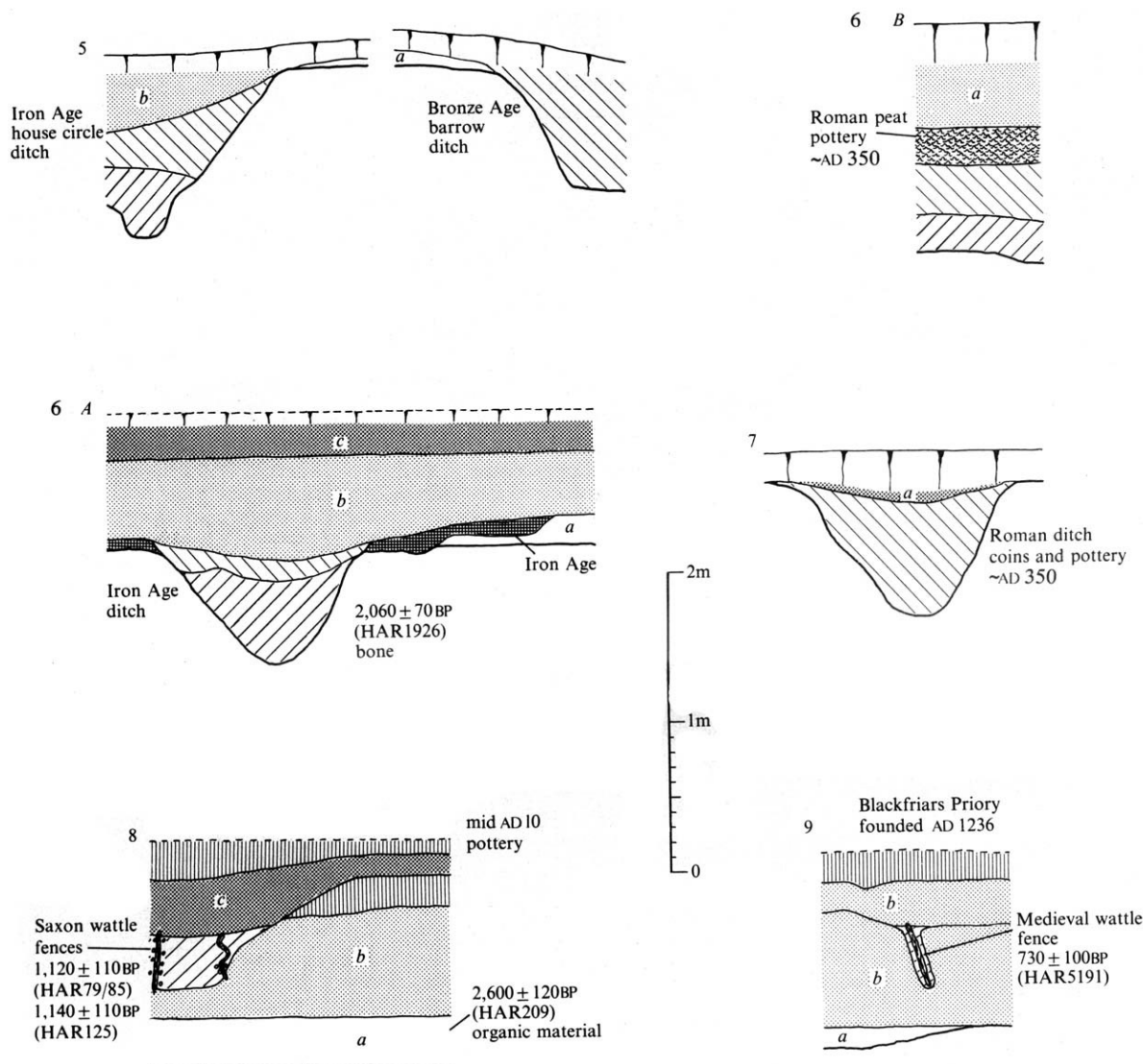


Fig. 3 Simplified composite sections of the alluvial exposures. Site 5, Port Meadow⁴³ (SP492085). *a*, Light-brown silty loam; *b*, gleyed clay. Site 6a, Farmoor⁴⁴ (SP443057). *a*, Yellow sandy silt; *b*, gleyed clay; *c*, clay loam. Site 6b, Farmoor (SP443057). *a*, Gleyed clay. Site 7, Claydon Pike (SU190996). *a*, Loam. Site 8, St Aldates, Oxford⁵ (SP513057). *a*, Reedswamp deposit of organic silt; *b*, gleyed clay; *c*, gleyed silty clays. Site 9, Blackfriars, Oxford⁴⁵ (SP512057). *a*, Undated, discontinuous, yellow sandy silt; *b*, gleyed clay.

methods, the winter sowing of cereals¹⁵ and river management will affect continuity of flow and thereby sediment transportation².

Correlation with archaeology

Discussion concentrates on those sub-catchments contributing most to the modern flood flow of the Thames at Goring, ~50% being from the Cotswolds, most of the rest being from the clay vales and gravel terraces²⁰. Along with almost all of the British Isles, the upper Thames valley developed a complete forest cover in the early Holocene²¹ and it is very unlikely that the hunters and gatherers of the Mesolithic had any impact on the hydrological cycle. From the distribution of long barrows and artefacts, the earliest Neolithic clearances in the area seem to have been mainly in the Cotswolds, one at Ascott-under-Wychwood being dated to ~5,000 BP²². Most agricultural clearances would have been small and not necessarily permanent; indeed, Ascott-under-Wychwood was abandoned to woodland²³. In the later Neolithic (~4,000 BP), activity was concentrated on the gravels, with major ritual complexes at Dorchester and Stanton Harcourt²⁴. The Thames gravels remained the focus of activity throughout most of the Bronze Age, and by 3,000 BP some parts of the gravel terraces were very open indeed; for example,

pollen analysis for a Bronze Age pond at Mount Farm, Dorchester, gave only 4% tree and shrub pollen and suggested a landscape predominantly of grassland (J. R. A. Greig, personal communication). There was relatively limited Bronze Age activity on the Cotswolds; most barrows occur in twos or threes rather than in large cemeteries of 20 to 30, as on the gravels^{25,26}. Until the late Bronze Age, human activity in the upper Thames valley was probably insufficient to have much effect on river flow or alluviation.

Starting in the late Bronze Age and continuing into the Iron Age, there was an increase in clearance and in the importance of arable agriculture. The density of occupation sites on the Thames gravels rose greatly in the Iron Age. Some had numerous grain storage pits²⁷ and late Bronze Age or early Iron Age plough marks have been found in the gravels. The gravel terraces are flat and free-draining, so the arable intensification on them would contribute little to the sediment load of the river.

In the Cotswolds many hillforts were constructed²⁸ and would have required a substantial labour force, implying a major investment of resources. Nevertheless, there is little evidence of dense occupation and the other scattered settlements are mostly small enclosed farms²⁹. Grain storage pits do not seem

to be numerous. These sites may thus be associated with extensive clearance mainly for pastoralism, with arable possibly restricted to the flatter plateaus. The resulting rise in water table on the floodplain and the onset of flooding by the middle Iron Age would thus not necessarily be accompanied by a significant increase in alluviation.

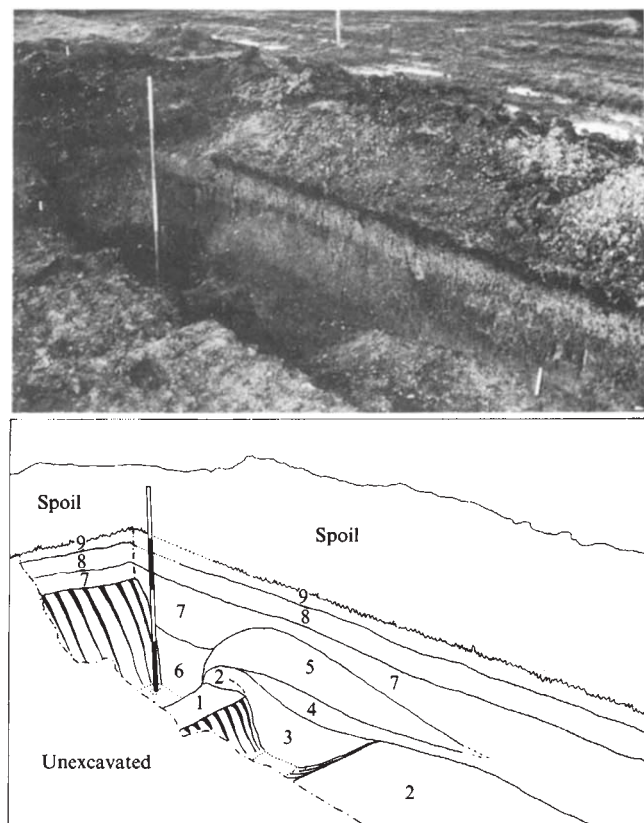


Fig. 4 The alluvial sequence at Drayton. 1, Undisturbed gravel; cream to yellow sand and gravel. 2, Neolithic ground surface and cursus bank; yellow to brown sandy clay loam; largely decalcified. 3, Filling of Neolithic cursus ditch; yellow-brown somewhat gravelly clay silt; slightly gleyed; very poor organic preservation at bottom. 4, Alluvium; dark grey clay; heavily gleyed. 5, Upcast from Roman ditch; yellow gravelly clay loam; slightly gleyed. 6, Filling of Roman ditch; dark grey-brown to black highly organic silt; good organic preservation. 7, Alluvium; dark grey clay; heavily gleyed. 8, Alluvium; pale buff clay loam; slightly gleyed. 9, Present-day A horizon: dark grey-brown humic clay loam.

Further agricultural intensification possibly began in the late Iron Age and certainly continued throughout the Roman period, when the Cotswolds became an area of agricultural importance, with many Roman villa estates^{30,31}. On two of these sites, Ditchley and Shakenoak, granaries have been excavated³², while a large 'Celtic field' system was laid out in association with the Barnsley Park villa³⁰. Other Roman field systems, Roman ploughsoils and substantial quantities of burnt cereal remains are known from the Cotswolds. This Roman activity would have exposed soils formerly under grass or woodland to erosion on an unprecedented scale. Roman agricultural activity remained intense on the gravels and settlement spread onto the clay slopes. Alluviation would have been further encouraged by arable expansion on the heavier soils and the introduction of ditched drainage and improved ploughs. Taken together, these factors provide a good explanation for the flooding and alluviation in the Roman period.

At the end of the Roman period the villa system collapsed³³. The forest of Wychwood grew up over some of the abandoned Cotswold villas³⁴, but mixed farming continued on the gravels.

From the mid-Saxon period onwards, an agricultural revival took place. Analysis of the Domesday survey gives the Cotswolds as the main arable area of the region³⁵ and throughout the late Saxon and early medieval periods assarting reduced the size of Wychwood. Alluviation was certainly taking place when late Saxon/early medieval agriculture was at its zenith. Medieval ridge and furrow cultivation, reflecting deeper ploughing and favouring rapid surface run-off, would have encouraged erosion and sediment transport. Surviving traces show that it was very extensive on the clay slopes³⁶.

With the decline in population at the Black Death in the second half of the fourteenth century AD, there was a general shift to grassland³⁷. Much of the clay land was not ploughed again until the twentieth century. The wool industry was already well established in the Cotswolds, and it rose to great prominence in the late medieval period³⁸. Alluviation had declined by about the end of the Middle Ages. There was no general reversion of agricultural land to woodland, however, and historical records show that flooding continued¹².

Conclusions

Flooding and alluviation on the Thames floodplain were not significant throughout the Holocene, but were largely restricted to the past 3,000 yr. Furthermore, the degree of flooding and alluviation has not been uniform within this short period. It is clear that human activity in the drainage basin provides an entirely adequate explanation for the changes since the early Holocene. Any climatic influence may have been completely obscured by the effects of human intervention. It is evident that alluviation was not a necessary accompaniment to flooding,

PERIOD	NEOLITHIC	BRONZE AGE	IRON AGE		ROMAN	SAXON	MEDIEVAL		POST-MEDIEVAL
Archaeology of limestone hills	Small scale settlement		First hillforts	Further settlement	Large villas develop	Economic collapse	Dense settlement	Depopulation, slow revival	
	Some agricultural clearances		? Extensive clearance	Pastoral emphasis	Much arable	Decline of arable	Arable very extensive	Reversion to grassland	
Archaeology of clay slopes	Little activity		? Settlement begins		Farms present	As for limestone hills			
River channels	Evidence for silting	No evidence for substantial movement							
Water table	Probably low	Low	Risen by c. 2,200 BP	Further rise	Remaining high				
Flooding	Little or none		Some sites dry ? Starting on others		Much of floodplain	? Continuing	Very extensive		
Alluviation	None		? Starting		Well under-way	? Reduction or cessation	Extensive-reaches some sites for first time	?	Little
Years BP	5,000/5,400	4,000	3,000	2,500	2,000	1,500	1,000	500	100

Fig. 5 Correlation of alluviation and hydrological conditions on the floodplain with human activity in the catchment.

which is an important consideration when dates obtained from deposits overlain by alluvium are used to interpret changes in hydrology and land use. In assessing the influence of human activity on erosion and alluviation, it has been important to consider technical changes in agriculture as well as land use.

The results are of wider relevance than to the Thames Valley alone. It is likely that a similar sequence of events, though probably not exactly synchronous, could be shown for many river valleys in lowland Britain³. For example, archaeological sites are known beneath alluvium on the floodplains of the Nene³⁹ and Ouse⁴⁰, while Shotton attributed a change in sedimentation on the middle Severn floodplain to post-Bronze Age arable activity⁴¹. Limbrey has sought more general correla-

tions between widespread changes in alluviation and agricultural developments³.

In terms of methodology, this study suggests that hydrological 'dating' of deposits on the basis of accretion rates can be of limited value: accretion was slow for much of the earlier Holocene when non-alluvial soil formation was important, and subsequently human activity had a variable impact on the rate of alluviation. Given the difficulty also of dating alluvial deposits directly by methods such as radiocarbon, archaeology is invaluable for palaeohydrology in providing otherwise unobtainable dating evidence. Furthermore, archaeological survey is essential for the assessment of the past impact of human activity in a drainage basin, without which any explanation of its post-glacial floodplain development is incomplete.

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Transduction and rearrangement of the *myc* gene by feline leukaemia virus in naturally occurring T-cell leukaemias

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Evidence of myc gene transduction by feline leukaemia virus in several spontaneous lymphoid tumours of cats suggests that recombinant viruses carrying oncogenes may be much more involved in oncogenesis in natural conditions than previously recognized.

TUMORIGENIC retroviruses can be conveniently subdivided into the strongly and weakly oncogenic. The strongly oncogenic viruses carry specific oncogenes, generally of cellular origin, responsible for the transforming function. The weakly oncogenic viruses, which generally induce leukaemias, have been thought

not to carry oncogenes. Based on this assumption, various explanations for tumour induction by the weakly oncogenic retroviruses have been put forward. Direct mechanisms that have been proposed include the mitogenic effects of replicative gene products on a rare target cell, typified by the autostimulation model of Weissman and co-workers¹, and the mutagenic effects of viral integration^{2–4}, while indirect mechanisms include immunosuppression or the induction of growth factors⁵. A number of mechanisms may operate in the development of even an

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individual tumour, as for most tumours multiple steps appear to be necessary for the fully malignant phenotype to be expressed^{6,7}.

Studies of tumours induced experimentally by weakly oncogenic avian retroviruses have led to the formulation of the model of insertional mutagenesis, in which the virus integrates adjacent to and activates a cellular oncogene²⁻⁴. The mechanism of activation is not fully understood but may involve alterations in transcriptional regulation or mutagenesis of adjacent gene (proto-oncogene) sequences. In some cases that have been investigated, transcriptional activation has resulted in the generation of a hybrid mRNA, initiating in the viral long terminal repeat (LTR) and running into the cellular gene. Alternatively, viral integration downstream or in the opposite transcriptional orientation from the gene may activate it via enhancer elements in the viral LTR. In the avian system, the *c-myc* gene is activated in bursal lymphomas²⁻⁴, and the *c-erb-B* gene in erythroblastosis⁸.

Feline leukaemia virus (FeLV), like the avian leukosis viruses, has generally been considered to belong to the class of weakly oncogenic retroviruses, carrying only replicative genes and no specific transforming gene. The majority of spontaneous lymphoid tumours in the cat are associated with FeLV infection. The tumours fall into two major groups; thymic or multicentric T-cell lymphosarcomas most of which are virus-positive, and alimentary lymphosarcomas of B-cell origin, the majority of which are virus-negative⁹⁻¹¹. In an analysis of FeLV proviruses in tumour DNA, we isolated and characterized a recombinant FeLV provirus carrying the *myc* oncogene. Consequently, we have examined *myc* gene alterations in 24 lymphoid tumours occurring in the cat population. Our results have revealed that out of 12 spontaneous virus-positive thymic lymphosarcomas, 6 have evidence of *myc* gene changes. Of these, five have *myc*-containing proviruses and only one has evidence of integration adjacent to *c-myc*. Rearrangement of the *c-myc* locus was seen in two out of four experimentally induced tumours.

Cloning of FeLV proviruses

As we thought the site of integration of FeLV may be important, it was helpful to identify tumours with only a small number of newly acquired (exogenous) proviruses. Most tumours contain multiple exogenous proviruses^{12,13}. Preliminary examination of our tumour series confirmed these results, but identified three tumours which appeared to contain only three to five copies of exogenous proviruses (T5, 84793 and 90412, see Table 1). The probe used was the U3 portion of the FeLV LTR (provided by J. Mullins, Harvard University) which detects only exogenous FeLV proviruses¹². We began cloning of proviruses from tumour 84793 which showed three U3-hybridizing *EcoRI* fragments, all greater than FeLV genomic length (see Fig. 3). From an *EcoRI* library of tumour 84793 DNA in bacteriophage λ gt.Wes we selected recombinants using the U3 probe. Eight recombinants yielded two unique clones corresponding to two of the three fragments seen on the original *EcoRI* digest. The *EcoRI* inserts were subcloned into the plasmid pAT 153, restriction maps were deduced, and FeLV sequences were mapped by hybridization and heteroduplex analyses.

One of the clones (CT8), 9.5 kilobases (kb) in length, appeared to contain a full length provirus with a restriction map typical of exogenous FeLV proviruses^{12,14,15}, while the other (CT4) contained approximately 6 kb of FeLV-hybridizing sequences, corresponding to the 5' portion of the genome. The distal 3' portion of the clone was unrelated to any cloned FeLV available (see Fig. 1), but detected an apparently single copy sequence in normal cat genomic DNA.

A *myc*-containing provirus

The proviral clones CT4 and CT8 were tested for homology with clones representative of a number of oncogenes: *abl*, *mos*, *src*, *K-ras*, *Ha-ras*, *sis*, *fes*, *fms*, *myc*, *myb*, *erb-A* and *erb-B*. The only positive hybridization recorded was that of CT4 with the *v-myc* clone. The 5' portion of the *v-myc* gene contains G+

C-rich sequences^{16,17} and hybridizes in low stringency conditions to many restriction fragments in mammalian DNA¹⁸ but we found however, that CT4 hybridized to the 5' *PstI*-*Sall* and the 3' *Sall*-*PstI* fragments of *v-myc* which correspond to the second and third exons respectively of the chicken and human *c-myc* genes (see Fig. 1), and not merely to the G+C-rich sequences contained in exon 2. To confirm that the sequences in CT4 were equivalent to the cat *myc* gene, we compared the restriction fragments of cat DNA related to the 3' end (*PstI*-*EcoRI* fragment) of the pCT4 clone and the 3' *Sall*-*PstI* fragment of *v-myc*. As can be seen from Fig. 2, the probes detect a common set of restriction fragments. These results indicate that the relatedness of CT4 is to the feline *myc* gene rather than some other cross-reactive sequence.

Analysis of restriction digests of clone pCT4 with probes specific for exon 2 (*v-myc* 5' *PstI*-*Sall*) and exon 3 (*v-myc* 3' *Sall*-*PstI* or *c-myc* *ClaI*-*EcoRI*) of *c-myc* shows that the sequences in pCT4 represent a processed form of *myc*. The pCT4 *myc* sequences are covalently linked to FeLV sequences and lack the intron sequences that would be expected in *c-myc* (Figs 1, 3). Assuming that the structure of feline *c-myc* proves to be similar to the chicken and human genes, as it appears to be from preliminary restriction mapping (Fig. 1), exons 2 and 3 of the normal locus are separated by around 1 kb of DNA^{17,19}. Furthermore, probes constructed from sequences upstream of the FeLV-related portion of pCT4 reveal a different set of restriction fragments in cat DNA, and show no relationship to the *c-myc* locus. Mapping of uncloned CT4 flanking sequences in tumour 84793 (Fig. 3) showed conserved restriction sites characteristic of an FeLV LTR (*SmaI*, *KpnI*) immediately 3' to the pCT4 *myc* sequences (see Fig. 1). The relatively high intensity of the low-molecular weight *HindIII*, *KpnI*, *SmaI* and *PstI* fragments in 84793 DNA may be explained if additional proviruses are present in this tumour. Unlike the pCT4 clone these may be present at different integration sites in individual tumour cells and hence do not contribute any additional resolved fragment when digestion is performed with an enzyme which cuts only once in the proviral sequence (for example, *EcoRI*). Instead, the additional copies give rise to a background smear corresponding to the many different junction fragments generated by *EcoRI* digestion.

As Fig. 3 shows, probing with U3 confirms that the *myc* sequences are linked to an FeLV LTR when digestion is performed with *KpnI* or *SmaI* which cut in the R region between U3 and U5 (refs 12, 14, 15), but digestion with *HindIII* or *PstI*, which also generate internal genomic fragments from the pCT4 provirus, separates the *myc* and U3-hybridizing sequences. Figure 3 also shows that tumour 84793 contains an excess of FeLV proviruses with restriction maps typical of conventional helper-type viruses (see Fig. 1).

In summary, the results show that tumour 84793 contains multiple copies of a *myc*-containing FeLV provirus, structurally analogous to MC29 avian myelocytomatosis virus¹⁶ only one of which is in a clonally-related integration site. The simplest interpretation is that tumour 84793 underwent superinfection after clonal expansion of a cell infected with a *myc*-containing provirus.

Transduction of *myc* by FeLV

It should be noted that digestion with *KpnI*, *SmaI* or *PstI* liberates internal genomic fragments including the *myc* sequences from the provirus represented by pCT4. In most cases, the boundary restriction sites are in FeLV sequences (see Fig. 1). Thus, digestion of cat tumour DNA with these enzymes and probing with *myc* provides a test for similar recombinant viruses. Another four independent tumours showed multiple rearrangements and, in some cases, amplifications of the *myc* sequences that indicate integrated proviruses of the type characterized by CT4 (Fig. 1). Digestion with appropriate restriction enzymes indicated that cases T11, 84929, F422 and T3 contain, respectively, one, two, four and five copies of *myc*-containing proviruses (Fig. 4a). The copy number is estimated by counting the

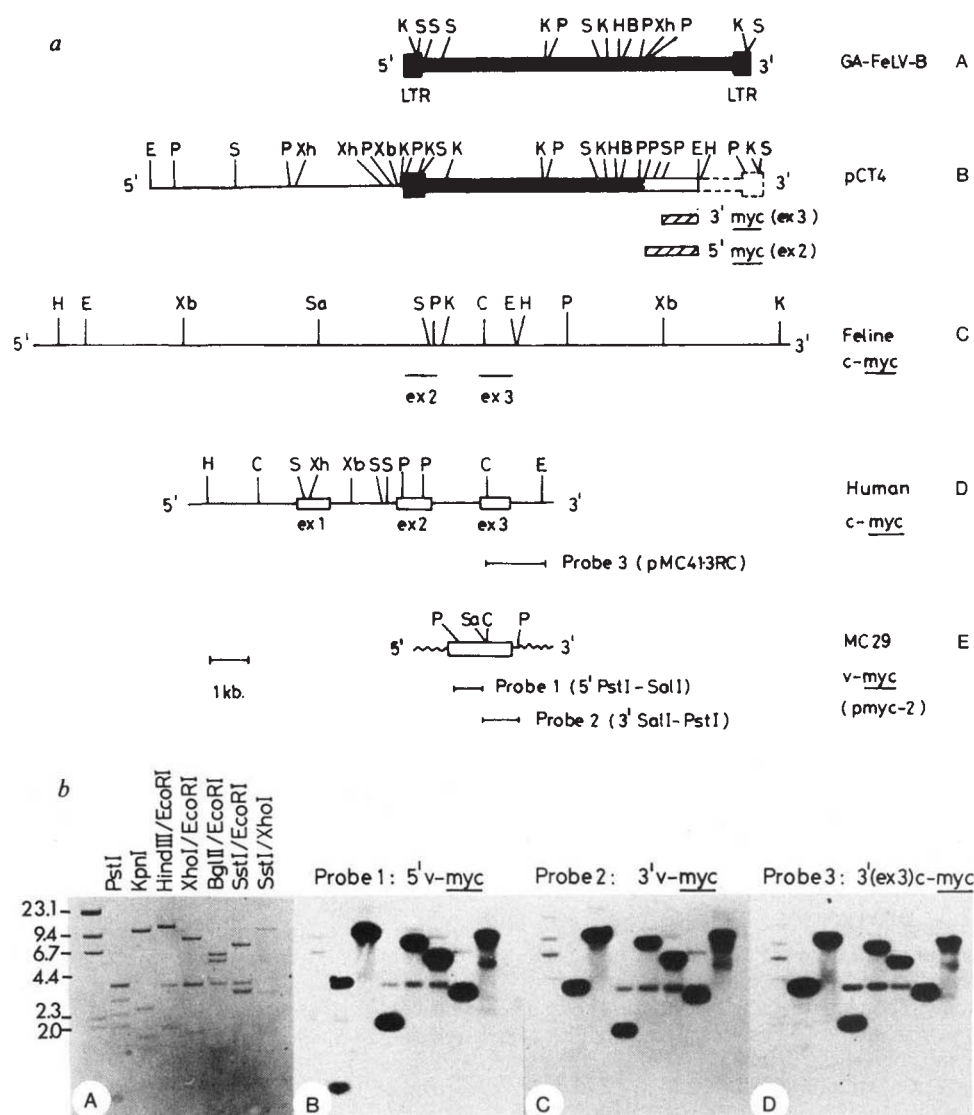


Fig. 1 **a**, Comparative restriction maps of clone CT4, FeLV and *c-myc* loci of human and feline genomes. A typical FeLV provirus is shown in A. This map is based on the pFGB clone of the Gardner-Arnstein strain of FeLV (GA-FeLV-B) published by Mullins and co-workers^{14,15}. Clone λ CT4 shown in B, was selected from an *EcoRI* library in λ gt.Wes. The 13.5 kb insert was subcloned into plasmid pAT153. FeLV-related sequences are indicated by block shading. Around 6 kb of FeLV-related sequences were detected by hybridization and heteroduplex analyses (C. Normand, unpublished observations). Restriction maps were deduced from double digestion and partial digestion analyses. The location of *myc*-hybridizing sequences (discussed in **b**) in pCT4 is indicated by hatched bars underneath. The broken lines at the 3' end indicate sequences in the tumour DNA outside the cloned region. The location of an LTR 3' to the *myc*-related sequences of pCT4 is indicated by analyses shown in Fig. 3. A partial physical map of the feline *c-myc* locus is presented in C. The restriction sites marked are those that could be deduced using 5' and 3' *v-myc* probes, corresponding to exons 2 and 3. The tentative location of exons 2 and 3 is based on these data and on extrapolation from the published sequence of human *c-myc*^{17,40,41}. The location of exon 1 is unknown. The human *c-myc* locus is shown in D and the subclone corresponding to the 3' exon indicated underneath. This subclone, pMC413RC, was kindly provided by Dr R. Gallo (NIH). The open blocks denote *myc* exon sequences. Finally, the subclone *pmyc* 2 from MC29 avian myelocytomatosis virus (from Dr J. M. Bishop) is illustrated in E, as are the fragments used to probe pCT4 for relatedness to *myc*. The 5' *PstI*-*SalI* and 3' *SalI*-*PstI* fragments of *pmyc*-2 correspond to exons 2 and 3 of *c-myc*. Restriction enzyme abbreviations: B, *Bam*HI, C, *Cla*I, E, *Eco*RI, H, *Hind*III, K, *Kpn*I, P, *Pst*I, S, *Sma*I, Sa, *Sal*I, Xb, *Xba*I, Xh, *Xho*I. **b**, Mapping of *myc*-related sequences of clone CT4. Restriction enzyme digests of pCT4 were prepared (panel A) and a series of identical blots were hybridized with the 5' *PstI*-*SalI* fragment of *v-myc* (probe 1, panel B), the 3' *SalI*-*PstI* fragment of *v-myc* (probe 2, panel C) or the 3' exon of human *c-myc* (probe 3, panel D). The results indicate that all the hybridizing sequences map to the extreme 3' end of the pCT4 insert. The only difference between the results for probes 1, 2 and 3 is that probe 1 detects an additional small *PstI* fragment. Otherwise, each probe detects the terminal *PstI*-*EcoRI* fragment of pCT4. Probing of cat DNA with the terminal *PstI*-*EcoRI* fragment detects predominantly exon 3 of *c-myc* (see Fig. 2) and we believe therefore that the junction of 5' and 3' *v-myc*-related sequences is closely 3' to the terminal *PstI* site of pCT4.

Methods: Specific probes were generated by nick-translation (to $\sim 1 \times 10^8$ c.p.m. μg^{-1}) of DNA fragments extracted from low melting point agarose gels. Hybridization was carried out at 42 °C in the presence of 50% formamide, 5 $\times$ SSC, 5 $\times$ Denhardt's solution, 0.1% SDS, 100 $\mu\text{g ml}^{-1}$ salmon sperm DNA and 0.025 M sodium phosphate (pH 7) at probe concentrations of 1 ng ml^{-1} . Blots were washed in 2 $\times$ SSC, 0.5% SDS at 60 °C (2 changes, 30 min each) and rinsed in 0.1 $\times$ SSC before drying and exposure to Kodak XAR or XRP films. Radioactive markers were prepared by end-labelling of *Hind*III-digested λ DNA. In panel A, DNA was visualized by staining with ethidium bromide.

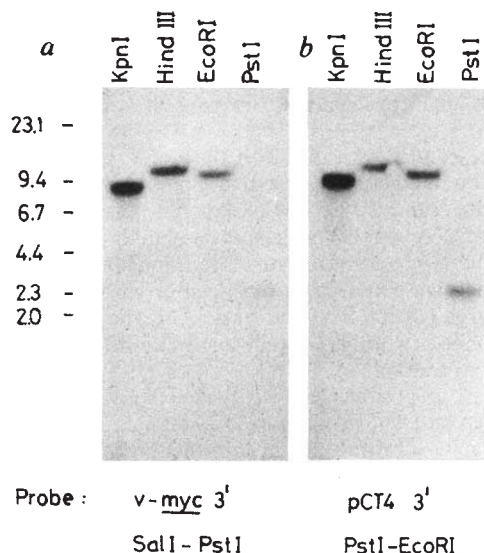


Fig. 2 Identity of feline genomic sequences detected by pCT4 *myc*-related sequences and MC29 *v-myc*. Normal cat thymus DNA was digested with *KpnI*, *HindIII*, *EcoRI* or *PstI*, blotted and hybridized with the *v-myc* *Sall*-*PstI* 3' fragment or the pCT4 *PstI*-*EcoRI* 3' fragment (see Fig. 1). Hybridization conditions were as outlined in Fig. 1b except that 10% dextran sulphate was included and probe concentrations of 5 ng ml⁻¹ were used. Identical hybridization conditions were used but the blots were washed in 0.1×SSC at 60 °C (a) and in 2×SSC at 60 °C for 1 h (b).

single copy-intensity fragments in addition to the normal *c-myc* locus when digestion is performed with an enzyme which fails to cut or cuts only once in the provirus (*EcoRI*, *HindIII* in some cases). Also, *KpnI*, *SmaI* and *PstI*, which have conserved sites in *myc* and/or FeLV LTRs, generate internal genomic fragments. Thus, a single abnormal fragment in addition to the normal *c-myc* fragment is detected after digestion with these enzymes. The intensity of hybridization of the novel fragment varies according to copy number. In contrast to tumour 84793,

the other four cases appear to contain predominantly or exclusively clonally integrated *myc* proviruses. Probing of the same tumour DNAs with U3 confirms the linkage of FeLV LTR and *myc* sequences in these cases (not shown) and also reveals an excess of viral copies with restriction maps typical of replication-competent FeLV (helper) viruses. In all of the cases presented in Fig. 4, these gave rise to discrete virus-host junction fragments suggesting clonal proviral integration.

In each case where we found FeLV/*myc* recombinant proviruses, we also detected the normal, unrearranged *c-myc* species at apparently normal intensity. If recombination at the DNA level with *c-myc* is a prerequisite for the generation of these viruses (see model proposed by Swanstrom and co-workers²⁰) it could be inferred that the novel *myc* sequences were transduced from some cell other than the final tumour cell.

Further evidence for the viral nature of the novel *myc* sequences came from analysis of the viruses released from the F422, T11 and T3 cell lines which exhibited encapsidation of *myc*-related RNAs (not shown). To demonstrate that these represented functional viruses, feline embryo cells were inoculated with culture supernatants from the cell lines or with blood plasma taken at necropsy. The embryo cells were subsequently grown to allow virus spread and were collected for DNA extraction. Digestion with *KpnI* released discrete *myc* fragments from the proviral structures that were distinguished by electrophoretic mobility from the *c-myc* digestion fragments. Analysis of infected feline embryo cell DNA showed that in three cases transfer of the *myc* sequence had taken place (Fig. 4b), providing the final link establishing the viral nature of the novel *myc* species in the lymphoid tumour cells. A summary of the cell lines and primary tumours in which *myc*-containing viruses were discovered is included in Table 1.

Other *myc* gene rearrangements

Of 16 virus-positive tumours examined (see Table 1), 3 showed *c-myc* gene rearrangements. Two of these cases are clearly consistent with viral integration around the *c-myc* locus. Comparison of Southern blots of tumour and control DNA showed a reduction in intensity of the band corresponding to the normal *c-myc* locus in the tumour DNA and the appearance of a new

Table 1 Alteration of the *myc* gene in feline leukaemias

Virus status	Field or experimental	Source of leukaemic cells	Case no. or code	<i>myc</i> involvement
Positive	Experimental	Thymic lymphosarcoma	T5	<i>c-myc</i> rearrangement
			T8	<i>c-myc</i> rearrangement
			T10	—
			Q109	—
			F422	<i>myc</i> provirus
		T-cell line	T3	<i>myc</i> provirus
			FL74	—
			T11	<i>myc</i> provirus
			84793	<i>myc</i> provirus
	Field	Thymic lymphosarcoma	84929	<i>myc</i> provirus
			90412	<i>c-myc</i> rearrangement
			84904	—
			86800	—
			84907	—
		Alimentary lymphosarcoma*	T14	—
			87416	—
			86503	—
			88043	—
Negative	Field	Thymic lymphosarcoma	89960	—
			75800	—
			83029	—
			87655	—
		Alimentary lymphosarcoma	B1	<i>c-myc</i> amplification
		B-cell lymphosarcoma†	87672	—
		Myelomonocytic leukaemia		

(—) Denotes none detected.

* Alimentary lymphosarcomas in the cat are almost always B-cell tumours.

† A case in which the primary tumour occurred in the spleen, with immature, immunoblastoid tumour cells.

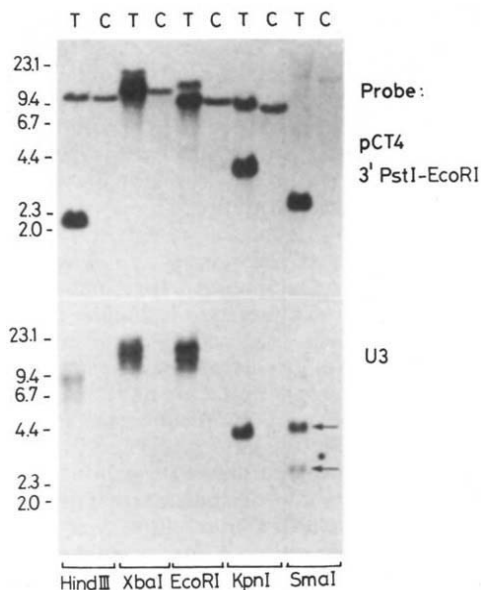


Fig. 3 Restriction endonuclease site mapping of *myc* and FeLV LTR hybridizing sequences in tumour 84793. A Southern blot of DNA from tumour 84793 (T) and a normal cat DNA (C) cut with various restriction enzymes was probed with the pCT4 3' *PstI*-*EcoRI* fragment which detects exon 3 of the normal *c-myc* locus and, in the tumour DNA, strongly hybridizing low molecular weight fragments with *HindIII*, *KpnI*, *SmaI* or *PstI*. As discussed in the text, we deduce from this blot and the map of pCT4 that tumour 84793 contains multiple copies of a recombinant provirus and that the high intensity, low molecular weight *myc*-hybridizing fragments represent the 3' end of this genome (upper panel). Also, the 13.5 kb *EcoRI* fragment corresponding to clone pCT4 can be seen, superimposed on a background smear which presumably arises from additional non-clonally integrated copies of the provirus. These results were confirmed and extended by washing the blot and probing with the U3 portion of the FeLV LTR (lower panel) which, as expected, detects internal genomic fragments with *KpnI* or *SmaI* but not with *HindIII*, *EcoRI* or *PstI*. Examination of the *SmaI* digest shows that the recombinant viral genome (indicated by the lower arrow) is linked to U3 sequences at its 3' end and also that the tumour contains an excess of FeLV proviruses with a restriction pattern characteristic of non-defective helper-type proviruses (upper arrow and see Fig. 1). *EcoRI* digestion reveals discrete bands suggesting clonal integration of two of these proviruses and again a background smear suggesting non-clonal integration.

band of equal intensity representing the rearranged locus (Fig. 5).

Cases 90412 and T8 showed rearrangement when digestion was performed with *HindIII* or *EcoRI* but not with *KpnI*, *SmaI* or *PstI* (Fig. 5a). This suggests disruption of the *c-myc* locus at, or upstream of exon 2 (see Fig. 1). Since FeLV proviruses generally lack *EcoRI* sites the increase in size of the *EcoRI* fragment is consistent with the integration of a possibly full-length FeLV provirus in 90412 and T8. Similarly, all known FeLV isolates have at least one internal *HindIII* site. On this basis, the alterations seen in the tumour DNA are again consistent with FeLV integration adjacent to *c-myc* (see Fig. 5a). In the case of 90412, the low proviral copy number allowed us to show that the rearranged *EcoRI* fragment containing the *myc* sequences also hybridizes to an LTR probe, confirming that the rearranged DNA fragment also contains viral sequences (Fig. 5b). Tumour T5 has undergone a more complex rearrangement. In T5, lack of rearrangement of *HindIII* and *EcoRI* fragments suggests no alteration in the 5' end of the gene. However, analysis of *KpnI* or *XbaI* digests suggests amplification as well as rearrangement of the 3' end of *myc*. Unlike the cases analysed in Fig. 4, there is no evidence that tumour T5 contains an FeLV/*myc* recombinant virus. The exact nature of the *myc* alteration in T5 will have to be determined after further molecular cloning. Viral integration far upstream or downstream

of *c-myc* would not be detected by the probes available to us. It is therefore possible that some of the cases in which *c-myc* appears normal have sustained an integration of FeLV close enough to affect the gene but far enough away to escape our detection.

In contrast to the results with the FeLV-positive tumours, examination of eight virus-negative tumours (virus-negative by the separate criteria of FeLV isolation from plasma and analysis of tumour DNA with U3 probes) showed no obvious rearrangement of the *myc* gene. Detected alterations of *myc* were confined to one lymphosarcoma of B-cell origin (B1, Table 1) in which a large portion of *c-myc* or possibly the entire locus had been amplified twofold. Chromosome duplication would be a possible explanation.

Not all virus-positive feline leukaemias involve obvious rearrangements of the *myc* gene. It is possible that some other oncogene may substitute for *myc* in this process. Examination of proviral integration sites in these cases may identify other genes of importance in feline leukaemia.

Discussion

Feline leukaemia has been important for our understanding of natural viral leukaemogenesis. A striking feature is horizontal transmission, shown to occur in FeLV-induced leukaemia^{21,22} and now generally acknowledged to be the most important route of transmission for those retroviruses that induce disease in their host species. It was therefore of interest to examine the role of integrated proviruses in FeLV-associated tumours and to test the validity of the model of insertional mutagenesis in this host-virus system.

Our results include a small number of cases in which the feline *c-myc* gene has been rearranged in a manner suggesting adjacent proviral integration. However, we find more examples in which defective, recombinant FeLV (dFeLV) has incorporated the *myc* sequence. Although only a small number of tumours induced experimentally have been obtained so far, two out of four cases showed disturbances in the *c-myc* locus. Our findings raise the question of whether naturally occurring avian bursal tumours or other retrovirus-associated tumours might also involve recombinant viruses rather than, or as well as, the integration next to *c-myc* detected in high incidence in experimentally derived tumours²⁻⁴.

The highly pathogenic nature of oncogene-containing viruses and their rare isolation have led to the assumption that they are not naturally infective²³. The various dFeLV we have detected may have been generated *de novo* in each case. If this is so, their somewhat similar restriction maps may reflect common points of recombination between FeLV and *c-myc* sequences. The alternative possibility is that dFeLV is transmitted among cats and the common features of their restriction maps reflect a common origin for the viruses. Of the five cases in which we detected dFeLV, one was a cell line isolated in Cornell in 1969 (ref. 24), while the others came from local sources. These sources were separated spatially and temporally. If horizontal transmission does occur, it must operate over a wide area and may not result in rapid induction of disease.

The clonal integration pattern of the dFeLV and FeLV proviruses in our tumour series contrasts with the high percentage of nonclonal integration of FeLV found previously by Casey and co-workers¹². The differences between our observations may be accounted for by the high percentage of cases of alimentary lymphosarcoma examined by Casey and co-workers. Our series contained only one such case and it too showed a non-clonal integration pattern. In contrast, all of the T-cell tumour DNA we examined contained some clonal integrated viruses as indicated by the discrete junction fragments detected with the U3 probe. This may indicate an important difference in the relationship of FeLV to the different tumour types. The absence of clonal integration suggests either that the virus has induced a polyclonal disease or that its role in tumour induction has been indirect, with clonal expansion of the tumour cells preceding viral infection. An important question is the biological

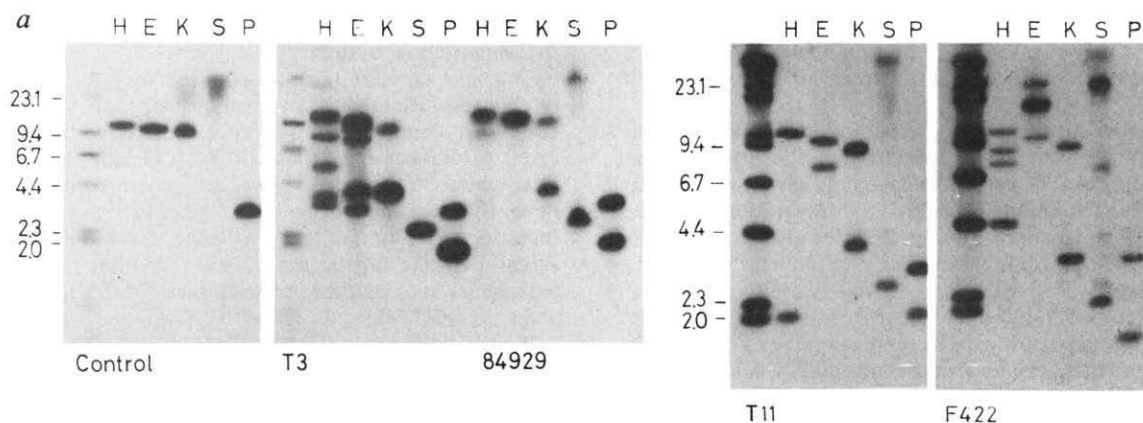


Fig. 4 a, Recombinant viruses in five independent tumours. The normal feline *c-myc* fragments detected by pCT4 3' or *v-myc* 3' are typified by the T11 control tissue shown in **a**. Single restriction fragments are seen with *HindIII*, *EcoRI*, *KpnI* or *PstI*, while *SmaI*, which cuts infrequently, shows a poorly resolved high molecular weight fragment. The probe used was the pCT4 3' *PstI*-*EcoRI* fragment and hybridization conditions were as outlined for Fig. 2. Four tumours show novel *myc* fragments similar to those seen in tumour 84793, bounded by common FeLV LTR and internal restriction sites suggesting the presence of clonally integrated *myc*-containing proviruses at one (T11), two (84929), four (F422) and five (T3) copies per cell. Digestion with enzymes which fail to cut or cut only once within the putative provirus (*EcoRI*, *HindIII* in some cases) yield different fragments for each copy, while LTR cutters (*KpnI*, *SmaI*, *PstI*) yield common fragments from each integrated copy. Probing with the 5' end of *v-myc* (not shown) confirms that the novel fragments represent a processed form of the *myc* gene. Restriction enzyme abbreviations: H, *HindIII*; E, *EcoRI*; K, *KpnI*; S, *SmaI*; P, *PstI*. **b**, Virus-mediated transfer of *myc* sequences. Feline embryo cells (FEA) were infected with virus-containing fluids from a variety of sources. In the cases of F422, T3 and T11 cultured T-lymphocytic cells were used for fresh virus collections (TCS). FL74 is another T-lymphocytic tumour cell line which releases FeLV but in which we detected no *myc* alteration. For cases 84793 and 84929 no cultured cells were available and virus isolation was attempted from plasma collected at necropsy. The embryo cells were subcultured and grown for 3 weeks to allow virus spread before collection and extraction of DNA. At this stage, no morphological transformation was seen. Cell DNA was digested with *KpnI* and the blot was probed with pCT4 *PstI*-*EcoRI* 3' fragment (Fig. 2). As can be seen by comparison with **a**, the novel *myc* hybridizing fragments in the infected cells correspond in size to those seen in the source tumours. Three of the tested sources provided successful transfer of proviral *myc* sequences.

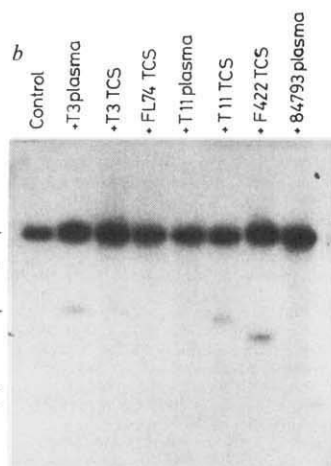
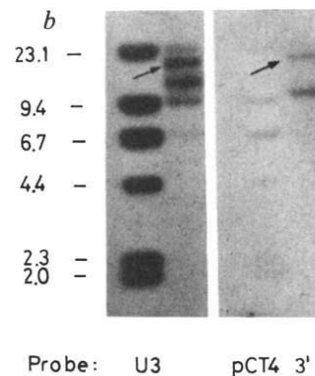
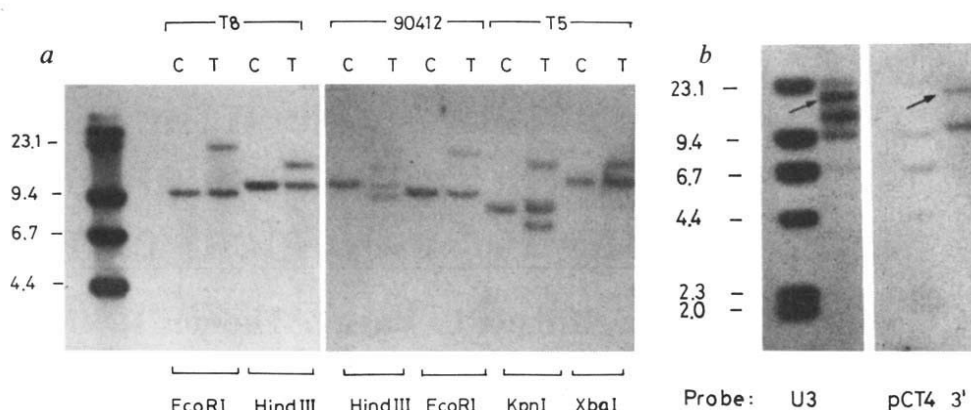


Fig. 5 Rearrangements of *c-myc* in independent feline leukaemias.

a, Tumour DNAs and control non-tumour tissue (kidney) DNAs were digested with restriction enzymes and probed with the pCT4 *PstI*-*EcoRI* 3' fragment (Fig. 1). Hybridization and washing conditions were as in Fig. 2, right panel. Tumour DNA is denoted by T, control tissue (kidney) by C. Tumours T8 and 90412 showed *myc* rearrangements with *HindIII* or *EcoRI*. Based on preliminary mapping of the feline *c-myc* locus, these alterations are consistent with integration of proviral information upstream of exon 2 in the cases of T8 and 90412. Tumour T5 has sustained a more complex alteration in which two or three new *myc* hybridizing *KpnI* fragments are resolved. Digestion with *XbaI*, however, shows a single novel fragment, larger than the normal *c-myc* species, and an increase in the intensity of the normal sized fragment. **b**, The coincidence of LTR (U3) and rearranged *myc*-hybridizing sequences is shown in tumour 90412. An *EcoRI* digest of tumour 90412 was probed with U3, the blot was washed and reprobed with pCT4 *PstI*-*EcoRI* 3' fragment. The common *myc* and U3 hybridizing fragment is indicated by arrows. The high exogenous proviral copy number in T8 prevented a similar analysis.



activity of the various dFeLV that we have identified. Infection of feline embryo cells has so far resulted in no obvious morphological transformation, in contrast to the effects of MC29 *v-myc* (ref. 25). Low expression or target cell specificity may explain our results. We are currently investigating transformation of bone marrow or thymic lymphocytes *in vitro* and are cloning the various dFeLV for further *in vitro* transformation studies. Recent studies show that thymotropism and other target cell specificities can be carried by the 3' end of MuLV, presumably the U3 region of the LTR (refs 26, 27). In view of results with

avian bursal lymphoma, where activation of *c-myc* and another oncogene, *Blym*, appear as discrete steps in the induction of this disease^{28,29}, it might be asked whether another gene is activated in feline leukaemias. We are investigating this possibility, but extensive testing of 10 of the tumours in the NIH 3T3 transformation assay has so far failed to show transfer of an activated feline oncogene.

It has been suggested that virus-negative cases of feline leukaemia might be induced by FeLV by a 'hit-and-run' mechanism³⁰. Although we found no comparable *myc* alterations in

eight virus-negative leukaemias, rearrangements may have occurred in regions outside the domain analysed in this study. Further experiments are required to investigate the possible role of FeLV in these cases.

Involvement of the *myc* gene in feline T-cell leukaemias casts further doubt on the tissue specificity of the *myc* oncogene. Previous reports of *c-myc* rearrangements have been restricted to B-cell leukaemias, mediated by viral integration in the case of avian bursal lymphomas and by translocation in mouse plasmacytomas³¹⁻³⁴ and human Burkitt's lymphomas^{34,35}. Viruses containing the *v-myc* gene induce a wide variety of tumours in birds including myeloid leukaemias, carcinomas and sarcomas²⁵. However, recent studies with recombinant viruses derived from MC29 show that viruses can be selected which cause predominantly lymphoid tumours. These tumours are also induced in bursectomized birds and the tumour cells carry T- or B-cell markers³⁶. Our results extend these findings and are the first

example in which either *c-myc* or *v-myc* can be implicated in the same tumour system.

The most surprising feature of our study is the high incidence of oncogene-containing viruses in primary tumours. Two other feline *myc*-containing viruses have been found by independent investigators working with FeLV (refs 37, 38). The established view would be that such viruses are generated only rarely and have a numerically insignificant role in naturally occurring tumours^{22,39}. Our findings challenge these assumptions and should provoke further examination of other virus-associated leukaemias such as those of wild mice (MuLV), cattle (BLV) and man (HTLV).

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Specific interaction between the self-splicing RNA of *Tetrahymena* and its guanosine substrate: implications for biological catalysis by RNA

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Splicing of the ribosomal RNA precursor of Tetrahymena has previously been shown to require no protein in vitro; the cleavage-ligation activity is intrinsic to the RNA molecule. Analysis of the reaction kinetics with guanosine, which is a substrate in the reaction, and with several guanosine analogues suggests that guanosine binds to a specific site on the pre-rRNA. It appears that the RNA, like an enzyme, binds its substrate to promote the rate and specificity of a biological reaction.

ENZYMES can be defined as biological macromolecules that accelerate the rates of specific biochemical reactions. The catalytic properties of enzymes result from their ability to bind to specific substrates in such a way that the activation energy for the reaction that they catalyse is lowered. Enzyme-substrate complexes are formed only transiently, and after catalysis the free enzyme is released.

Proteins are especially well suited to be biological catalysts because they can provide a three-dimensional active site by

assuming a precise tertiary structure. Ribonucleic acids also fold into specific three-dimensional shapes, as, for example, has been demonstrated crystallographically for tRNA molecules^{1,2}. It thus seems possible that an RNA molecule could fold in such a way as to generate an active site for biological catalysis. Several enzymes, such as RNase P, 1,4- α -glucan branching enzyme and potato *o*-diphenol oxidase, have RNA components essential for their catalytic activities³⁻⁵. The peptidyl transferase activity of ribosomes also requires an RNA-protein complex^{6,7}. It remains

to be seen whether the RNA is directly involved in the active site of any of these ribonucleoprotein enzymes.

The rRNA precursor (pre-rRNA) of *Tetrahymena thermophila* is an extreme example of a reactive RNA molecule, no proteins being required for the cutting and ligation reactions that remove the intervening sequence from the pre-rRNA to take place *in vitro*⁸. The reaction requires a micromolar amount of a guanosine molecule, which is covalently linked to the 5' end of the intervening sequence (IVS) RNA during its excision⁹. After splicing, the excised IVS RNA circularizes itself in another cleavage–ligation reaction¹⁰. The circular molecule retains the cleavage–ligation activity, as evidenced by its ability to undergo specific reopening and reverse reactions (A. Zaug, J. Kent, F. Sullivan and T.C., manuscripts in preparation).

The self-splicing *T. thermophila* pre-rRNA thus has distinct enzyme-like properties⁸. It is able to lower the activation energy for cleavage–ligation reactions at precise sites along the RNA; only 2 of the 6,400 phosphodiester bonds in the pre-rRNA undergo cleavage–ligation during the splicing reaction. Its activity depends on a precise structure. It also seems likely that the pre-rRNA molecule has an active site which excludes water molecules and thereby prevents hydrolysis whilst allowing transesterification¹¹. Evidence is presented here that the pre-rRNA molecule is highly specific for its guanosine substrate. Furthermore, an analysis of the reaction kinetics indicates that the binding of guanosine to a specific site on the pre-rRNA facilitates the splicing reaction.

Pre-rRNAs react intramolecularly

Splicing of the pre-rRNA *in vitro* requires three factors: a monovalent cation, a divalent cation (Mg^{2+} or Mn^{2+}) and the guanosine substrate. In all assays the production of IVS with time ($d[IVS]/dt$) was measured in a standard splicing solution at constant pH, temperature, salt concentration and Mg^{2+} concentration. The concentration of either the unspliced rRNA precursor or the guanosine substrate was varied to determine how the reaction rate depended on these two factors. The IVS excision assay is a direct measure of two cleavages and one ligation—the addition of the guanosine. It has recently been shown by dideoxynucleotide sequencing that precise ligation of the exons accompanies IVS excision¹². We therefore expect that the rate of IVS excision is a reasonable measure of the rate of the entire splicing reaction.

At constant guanosine concentration the rate of IVS excision was first order with respect to pre-rRNA concentration (Fig. 1). Since $[G] \gg [pre-rRNA]$, the reaction can be described by a pseudo-first order rate equation in which the pseudo-first order rate constant, k_{obs} , is dependent on the concentration of guanosine:

$$v_t = d[IVS]/dt = k_{obs}([IVS]_{\infty} - [IVS]_t) \quad (1)$$

where $[IVS]_{\infty} = [pre-rRNA]_0$. At time zero, before any IVS has been excised, we have:

$$v_0 = k_{obs}[IVS]_{\infty} = k_{obs}[pre-rRNA]_0 \quad (2)$$

Figure 1c shows that pseudo-first order kinetics were maintained over a 40-fold variation of pre-rRNA concentration. The k_{obs} for the six points was $0.59 \pm 0.05 \text{ min}^{-1}$ (mean $\pm$ s.d.).

If the pre-rRNA participated in the splicing of other pre-rRNA molecules, the reaction would be expected to be second order with respect to $[pre-rRNA]$. Similarly, if any of the RNA products of splicing served as diffusible splicing factors, the reaction would be greater than first order. The observed first order dependence is most easily interpreted as an indication that each pre-rRNA acts intramolecularly to lower the activation energy for its own splicing.

Evidence for a guanosine binding site

To determine the dependence of the rate of IVS excision on the concentration of guanosine, k_{obs} was determined from semi-logarithmic plots (see Fig. 1 legend) for guanosine concentrations ranging from 0.1 to 200 μM (Fig. 2). As shown in Fig. 2c,

there is a hyperbolic relationship between k_{obs} and $[G]$. At low $[G]$ the rate of splicing is first order with respect to $[G]$, while at high $[G]$ the reaction rate becomes independent of $[G]$ and approaches a limiting velocity.

The reaction kinetics exemplified in Fig. 2 are typical of enzyme-catalysed reactions. Such kinetics are most easily explained in terms of an enzyme–substrate complex or, in this case, a pre-rRNA–guanosine complex. According to such an interpretation, the splicing reaction reaches a limiting velocity (V_{max}) at high $[G]$ because a guanosine binding site on the pre-rRNA has been saturated. However, such a kinetic analysis does not prove the existence of a binding site.

To determine the specificity of the pre-rRNA for its guanosine substrate, the ability of various guanosine analogues to promote the excision of the IVS in the standard splicing reaction conditions was investigated. The amount of IVS produced with each analogue was compared with the amount produced with the same concentration of guanosine. The results of these experiments are summarized in Fig. 3.

The analogues fall into three categories: (1) those that do not promote IVS excision; (2) those that do promote IVS excision but are required at a higher concentration than guanosine; and (3) those that are active at the same concentration as guanosine. Compounds in these three categories are denoted in Fig. 3 as $-$, $+$ and $++$, respectively.

Nucleosides modified at the 2'- or 3'-hydroxyl of the ribose sugar were inactive in splicing. Substitution at the 5'-hydroxyl, farther away from the reaction site, produced analogues that were as effective as guanosine in splicing. Similarly, modifications on the imidazole ring did not affect the amount of IVS excised. Modification or removal of any of the exocyclic substituents of the six-membered ring was found to decrease splicing activity. For example, there was no splicing with isoguanosine, which has the carbonyl and amino groups of guanosine interchanged, xanthosine, which has the amino group replaced by a carbonyl group, or purine ribonucleoside, which has no exocyclic substituents. Other modifications, such as monomethylation or elimination of the amino group, generated analogues that were competent in splicing, but were required at higher concentrations than guanosine.

Splicing presumably involves a nucleophilic attack of the 3'-hydroxyl of guanosine on the phosphate of the 5' splice site¹⁰. Thus, it is not surprising that modifications of the 3'-hydroxyl that decrease the nucleophilicity of the oxygen eliminate splicing. The inactivity of xyloguanosine suggests that the orientation of the 3'-hydroxyl is also critical.

The absence of splicing when the 2'-hydroxyl is modified could be explained in several ways. First, the proximity of the 2'-hydroxyl to the reaction site means that the 2'-hydroxyl could have electronic effects that would enhance reactivity of the 3'-hydroxyl. For example, the pK_a of ribose is lower than the pK_a of deoxyribose¹³. Second, the 2'-hydroxyl could be involved in non-covalent binding of guanosine to the RNA, helping to position it for reaction at its 3'-hydroxyl. It seems unlikely, however, that loss of a single hydrogen bond or van der Waals interaction could change the binding constant enough to eliminate splicing completely. Finally, the 2'-hydroxyl could form a covalent bond in an intermediate step of the splicing reaction. While such direct participation of the 2'-hydroxyl is common in RNA cleavage reactions, all known mechanisms result in RNA chains with phosphates at their 3' end¹¹. Cleavage of the pre-rRNA leaves the phosphate at the 5' end¹⁰, so if the 2'-hydroxyl is directly involved in rRNA splicing, a novel mechanism must be involved.

Modifications on the guanine base moiety would not be expected to directly influence the reactivity of the 3'-hydroxyl. The results with these analogues therefore suggest that the guanine base, in particular the six-membered ring, is responsible for binding the nucleoside to a site on the pre-rRNA. Specifically, the results suggest that optimum binding is achieved with a hydrogen bond acceptor at C-6 and a substituent capable of donating two hydrogen bonds at C-2. The results with 1-methyl-

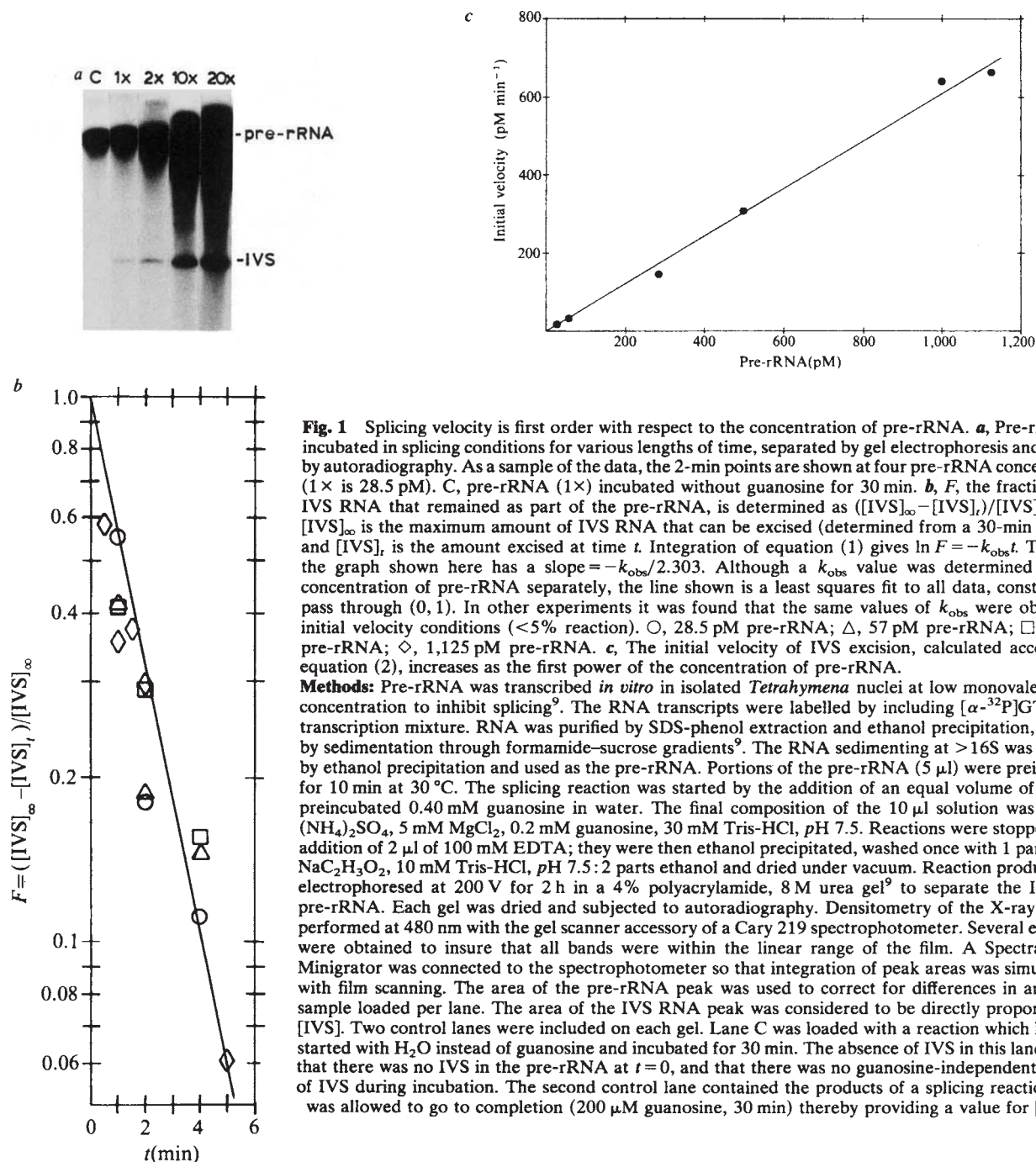


Fig. 1 Splicing velocity is first order with respect to the concentration of pre-rRNA. **a**, Pre-rRNA was incubated in splicing conditions for various lengths of time, separated by gel electrophoresis and detected by autoradiography. As a sample of the data, the 2-min points are shown at four pre-rRNA concentrations (1× is 28.5 pM). **b**, F , the fraction of the IVS RNA that remained as part of the pre-rRNA, is determined as $([IVS]_{\infty} - [IVS]_t) / [IVS]_{\infty}$, where $[IVS]_{\infty}$ is the maximum amount of IVS RNA that can be excised (determined from a 30-min reaction) and $[IVS]_t$ is the amount excised at time t . Integration of equation (1) gives $\ln F = -k_{\text{obs}}t$. Therefore, the graph shown here has a slope $= -k_{\text{obs}}/2.303$. Although a k_{obs} value was determined for each concentration of pre-rRNA separately, the line shown is a least squares fit to all data, constrained to pass through (0, 1). In other experiments it was found that the same values of k_{obs} were obtained in initial velocity conditions (<5% reaction). $\circ$, 28.5 pM pre-rRNA; Δ , 57 pM pre-rRNA; $\square$, 285 pM pre-rRNA; $\diamond$, 1,125 pM pre-rRNA. **c**, The initial velocity of IVS excision, calculated according to equation (2), increases as the first power of the concentration of pre-rRNA.

Methods: Pre-rRNA was transcribed *in vitro* in isolated *Tetrahymena* nuclei at low monovalent cation concentration to inhibit splicing⁹. The RNA transcripts were labelled by including $[\alpha\text{-}^{32}\text{P}]\text{GTP}$ in the transcription mixture. RNA was purified by SDS-phenol extraction and ethanol precipitation, followed by sedimentation through formamide-sucrose gradients⁹. The RNA sedimenting at $>16\text{S}$ was collected by ethanol precipitation and used as the pre-rRNA. Portions of the pre-rRNA (5 μl) were preincubated for 10 min at 30 °C. The splicing reaction was started by the addition of an equal volume of similarly preincubated 0.40 mM guanosine in water. The final composition of the 10 μl solution was 100 mM $(\text{NH}_4)_2\text{SO}_4$, 5 mM MgCl_2 , 0.2 mM guanosine, 30 mM Tris-HCl, pH 7.5. Reactions were stopped by the addition of 2 μl of 100 mM EDTA; they were then ethanol precipitated, washed once with 1 part 50 mM $\text{NaC}_2\text{H}_3\text{O}_2$, 10 mM Tris-HCl, pH 7.5:2 parts ethanol and dried under vacuum. Reaction products were electrophoresed at 200 V for 2 h in a 4% polyacrylamide, 8 M urea gel⁹ to separate the IVS from pre-rRNA. Each gel was dried and subjected to autoradiography. Densitometry of the X-ray film was performed at 480 nm with the gel scanner accessory of a Cary 219 spectrophotometer. Several exposures were obtained to insure that all bands were within the linear range of the film. A Spectra-Physics Minigrator was connected to the spectrophotometer so that integration of peak areas was simultaneous with film scanning. The area of the pre-rRNA peak was used to correct for differences in amount of sample loaded per lane. The area of the IVS RNA peak was considered to be directly proportional to $[\text{IVS}]$. Two control lanes were included on each gel. Lane C was loaded with a reaction which had been started with H_2O instead of guanosine and incubated for 30 min. The absence of IVS in this lane verified that there was no IVS in the pre-rRNA at $t=0$, and that there was no guanosine-independent excision of IVS during incubation. The second control lane contained the products of a splicing reaction which was allowed to go to completion (200 μM guanosine, 30 min) thereby providing a value for $[\text{IVS}]_{\infty}$.

guanosine are consistent with another hydrogen bond donor at N-1. However, splicing is very inefficient with 1-methylguanosine (IVS barely detectable at 0.2 mM), suggesting that steric hindrance by the N-1 methyl may preclude hydrogen bonding of neighbouring groups. Such steric hindrance has been invoked to explain why there is little or no hydrogen bonding between 1-methylguanosine and cytosine¹⁴.

When unspliced pre-rRNA was incubated in splicing conditions with either ^{14}C -guanosine or ^{14}C -inosine, labelled IVS RNA was detected by fluorography (data not shown). We therefore infer that all compounds that mediate the splicing reaction do so in the same way as GTP, that is by becoming covalently linked to the 5' end of the IVS RNA during its excision.

K_m values of guanosine analogues

To compare the efficiency of the guanosine analogues as splicing substrates in terms of quantitative kinetic parameters, it is necessary to assume a kinetic mechanism. The specificity for

guanosine and the hyperbolic relationship between k_{obs} and $[\text{G}]$ led us to suggest that the pre-rRNA has a binding site for guanosine, and that a pre-rRNA·G complex contributes to the self-splicing activity. A reaction mechanism that involves formation of such a complex and that is consistent with the kinetic data can be described with three rate constants:



A steady-state assumption for $[\text{pre-rRNA} \cdot \text{G}]$ leads to the Michaelis-Menten equation:

$$v_0 = \frac{V_{\text{max}}[\text{G}]}{[\text{G}] + K_m} \quad (4)$$

in which $V_{\text{max}} = k_2 [\text{pre-rRNA}]_0$ and $K_m = (k_{-1} + k_2) / k_1$. G can refer to guanosine or any other splicing-competent substrate. Since $[\text{pre-rRNA}]$ is changing during the reaction, the maximum velocity (V_{max}) occurs only at initial time. This differs from the

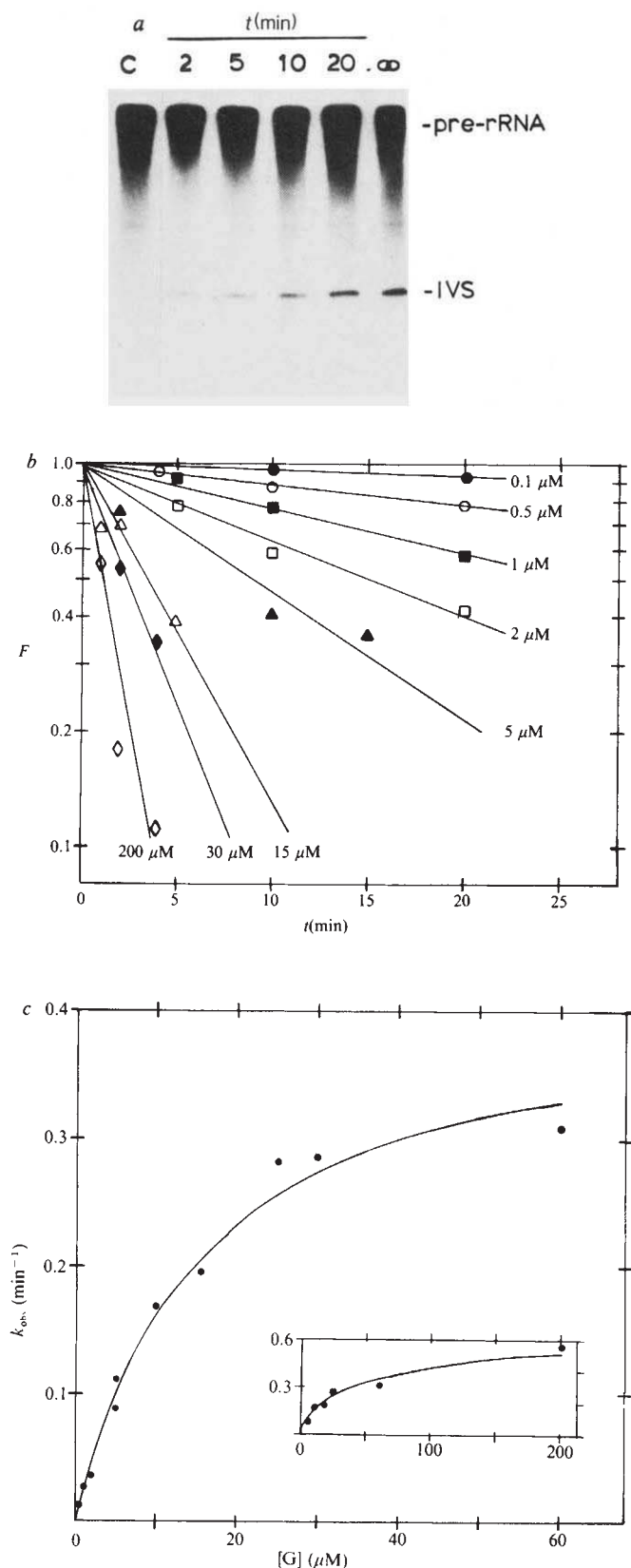


Fig. 2 A hyperbolic relationship exists between k_{obs} and $[G]$. **a**, Pre-rRNA was incubated in splicing conditions and analysed as in Fig. 1a, except $[G] = 5 \mu\text{M}$. ∞ , Pre-rRNA incubated at $[G] = 200 \mu\text{M}$ for 30 min to ensure complete splicing. **b**, Semilog plot of data from **a**, and similar data for reactions at different $[G]$: $\bullet$, $0.1 \mu\text{M}$; $\circ$, $0.5 \mu\text{M}$; $\blacksquare$, $1 \mu\text{M}$; $\square$, $2 \mu\text{M}$; $\blacktriangle$, $5 \mu\text{M}$; $\triangle$, $15 \mu\text{M}$; $\blacklozenge$, $30 \mu\text{M}$; $\diamond$, $200 \mu\text{M}$. Lines are least-squares fits constrained to pass through (0, 1). **c**, k_{obs} , calculated from the slope of the semilog graphs, is plotted against $[G]$. Inset includes k_{obs} at $200 \mu\text{M}$ guanosine.

situation with an enzyme in which the total enzyme concentration does not change during the reaction.

Equation (3) outlines the simplest splicing mechanism that involves pre-rRNA·guanosine complexation and also follows the Michaelis-Menten rate law. However, mechanisms of greater complexity, but that still involve a pre-rRNA·G complex, could also give the observed kinetics. In these cases the values of K_m and V_{max} would not change but the constants would be defined by a different combination of rate constants and concentrations.

Two of the splicing-competent guanosine analogues, inosine (I) and 2-aminopurine ribonucleoside (2APr), were subjected to a more extensive kinetic analysis. As with guanosine, a hyperbolic relationship between k_{obs} and substrate concentration was obtained. Lineweaver-Burk plots for three splicing substrates are shown in Fig. 4, and the kinetic parameters obtained are listed in Table 1. Although the K_m values for I and 2APr are approximately 100-fold higher than the K_m for guanosine, the k_2 (k_{cat}) values are the same within experimental error.

Therefore, it appears that the pre-rRNA discriminates among the various nucleoside substrates according to their free energies of binding. The substrates that bind the best have the lowest values of K_m . Once the nucleoside is bound to the RNA, its reactivity is independent of its base moiety, as evidenced by the equivalent values of V_{max} seen for G, I and 2APr.

Competitive inhibition studies

As a further test for the binding site model, several analogues were assayed for activity as competitive inhibitors. No inhibition of splicing was observed, however, with 2'-dGTP, 2',3'-ddGTP, xyloguanosine, araguanosine or 2'-O-methylguanosine present at a 500-fold excess of analogue to guanosine. In addition, no inhibition was seen when 3'-O-methylguanosine was present at a 200-fold excess. Thus, if these compounds bind to the site at all, they have very low affinity in the standard temperature and buffer conditions. These results could indicate that the binding site has strict requirements in the vicinity of the 2'- and 3'-hydroxyls.

Although no competitive inhibitor was found, a mixed substrate experiment demonstrated that two substrates can compete for the binding site. Samples of ^3H -labelled pre-rRNA were incubated with 0.005 mM of a ^{32}P -labelled guanosine compound in the presence or absence of a second nucleoside which was unlabelled. By monitoring the generation of ^{32}P -end labelled IVS it was possible to measure splicing which involved the guanosine compound separately from that which involved the additional substrate. As shown in Fig. 4c, there was little or no inhibition by adenosine at a concentration of 3.5 mM . Thus adenosine, which is not a splicing substrate, is also not a competitive inhibitor. In the presence of 3.5 mM inosine, the initial rate of ^{32}P -IVS RNA production was reduced by 53%. This value agrees well with that predicted if the reaction followed competitive inhibition kinetics. For competitive inhibition:

$$\text{Fractional inhibition, } i = \frac{[I]_0/K_i}{1 + [I]_0/K_i + [S]_0/K_m} \quad (5)$$

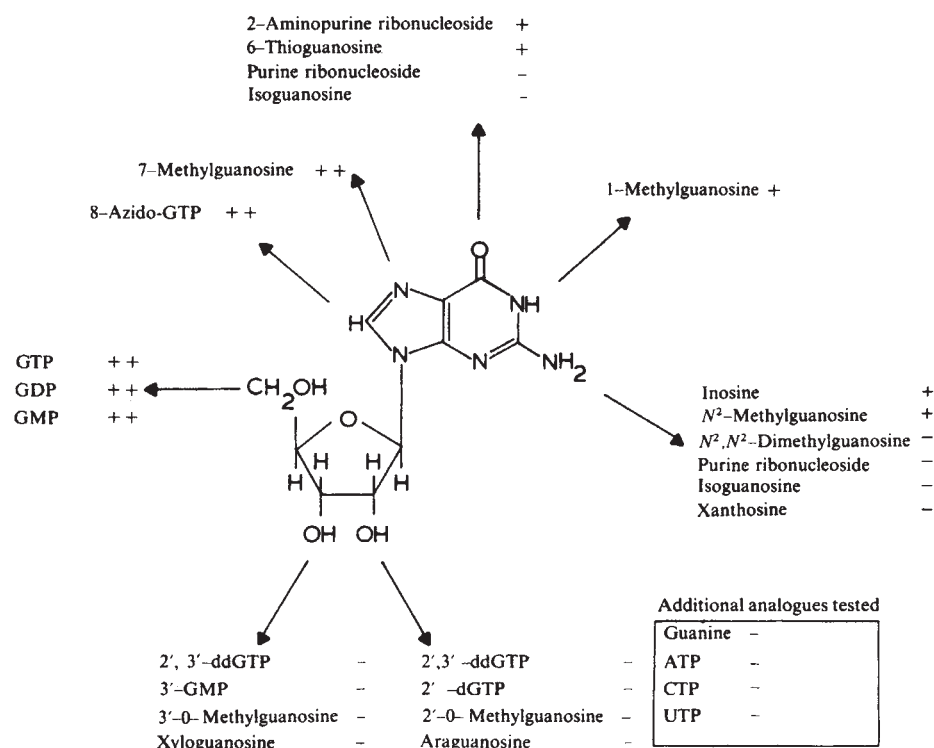
where I and K_i refer to the inhibitor and its K_m , and S and K_m refer to the substrate and its K_m . Based on this equation and the K_m values we have determined, a 50% inhibition would be predicted at the concentrations of substrate (guanosine compound) and inhibitor (inosine) used. A similar experiment was performed with 0.005 mM ^{32}P -GTP and 10.4 mM inosine; 75% inhibition was predicted and 78% inhibition was observed (data not shown).

Guanosine binding site

A model for the nucleoside binding site on the pre-rRNA is presented in Fig. 5. The proposal that there are four hydrogen bonds between guanosine and the pre-rRNA is derived from a consideration of the kinetic data. According to the mechanism of equation (3), if it is assumed that $k_2 \ll k_{-1}$, then K_m is approximately equal to the dissociation constant, K_d . The free

Fig. 3 Splicing activity of guanosine analogues. —, No detectable excision of IVS RNA; +, excision of IVS RNA required a substantially higher concentration of the analogue than of guanosine; ++, excision of IVS RNA occurred at concentrations similar to those of guanosine.

Methods: Splicing reactions were performed for 15 min as described in Fig. 1 legend, except that guanosine analogues were substituted for guanosine. Each analogue was tested for IVS excision activity at a concentration of either 100 μ M or 200 μ M and compared with an identical concentration of guanosine. After electrophoresis the amount of IVS produced was qualitatively compared. If the analogue did not show splicing activity at 100–200 μ M, it was tested at 1 mM. If there was no activity (<0.1% of the activity of guanosine) at 1 mM, it was designated —. Analogues that produced IVS RNA at 100–200 μ M were purified to ensure contaminating guanosine was not present and then retested. Purification was accomplished by reversed-phase HPLC using a μ Bondapak C₁₈ column. For 7-methylguanosine, inosine, xanthosine, uridine, 1-methylguanosine and xyloguanosine, elution was isocratic with 5% acetonitrile in 0.1 M triethylammonium acetate, pH 7.0 at a flow rate of 2 ml min⁻¹ (ref. 36). For 2-aminopurine ribonucleoside, N²-methylguanosine and 6-thioguanosine, elution was by linear gradient from 0.02 M KH₂PO₄, pH 5.5 to 60% methanol in water in 87 min at a flow rate of 1 ml min⁻¹ (ref. 37).



energy of binding can then be calculated for each substrate using the relationship $\Delta G = -RT \ln K_a$, where $K_a = 1/K_d$. For guanosine binding $\Delta G = -6.5 \pm 1.2$ kcal mol⁻¹, for inosine binding $\Delta G = -3.6 \pm 0.9$ kcal mol⁻¹ and for 2APr binding $\Delta G = -3.7 \pm 0.8$ kcal mol⁻¹. In addition to hydrogen bonding, other interactions, such as base stacking, van der Waals contacts and solvent interactions, could affect the free energy of binding. To a first approximation, however, the difference in binding free energy that occurs when guanosine is replaced by inosine ($\Delta\Delta G = 2.9$ kcal mol⁻¹) can be attributed to the loss of interactions with the amino group. Similarly, the difference between guanosine and 2APr ($\Delta\Delta G = 2.8$ kcal mol⁻¹) can be attributed to the carbonyl group and the proton on N-1. The data are therefore consistent with four hydrogen bonds (Fig. 5). Inosine and 2APr would each bind to the pre-rRNA with two hydrogen bonds. The average free energy per hydrogen bond, 1.4 kcal mol⁻¹, is well within the expected range. Such an analysis in no

way excludes the possibility of additional binding interactions. For example, base stacking could be very important, but if it stabilized the binding of two nucleosides to similar extents, it would make no contribution to $\Delta\Delta G$.

It is not difficult to envision how a nucleoside binding site could accelerate the reaction. A binding site can increase the effective concentration of reactants to approximate an intramolecular reaction. More specifically, precise positioning of the 3'-hydroxyl group of guanosine in proximity to the phosphate at the splice site could facilitate the first transesterification reaction required for rRNA splicing. Future work will be directed toward locating the guanosine binding site in the structure of the folded RNA molecule.

RNA as a biological catalyst

In Table 1, the kinetic parameters for the *Tetrahymena* pre-rRNA are compared with those of a number of other biological

Table 1 Kinetic parameters of pre-rRNA self-splicing and selected enzyme-catalysed reactions

Biological catalyst	Substrate	K_m (mM)	k_{cat} (min ⁻¹)	k_{cat}/K_m (M ⁻¹ min ⁻¹)
Pre-rRNA	Guanosine	0.021 ± 0.004	0.52 ± 0.15	24.8×10^3
	Inosine	2.8 ± 0.7	0.35 ± 0.03	0.13×10^3
	2APr	2.2 ± 0.5	0.34 ± 0.04	0.15×10^3
Pancreatic RNase	CpC	4.0*	14,400*	$3,600 \times 10^3$
	C>p	3.0†	330†	110×10^3
RNase T ₁	GpA	0.055	5,760	104.7×10^6
RNase P	Pre-tRNA ^{tyr}	10^{-5}	2–4	$200\text{--}400 \times 10^6$
T ₄ RNA ligase	ATP	0.0002‡	—	—
	ATP	0.012§	—	—

K_m and k_{cat} (k_2) values for the pre-rRNA self-splicing reaction at 30 °C in standard splicing solution were obtained by a nonlinear least squares fit to equation (4) using an analysis program based on the Marquardt algorithm³¹. Kinetic parameters for other biological catalysts were obtained from the following sources: pancreatic RNase, ref. 32; RNase T₁, ref. 33; RNase P, ref. 34 and C. Guerrier-Takada and S. Altman, personal communication; T₄ RNA ligase, ref. 35.

* Formation of 2',3' cyclic phosphate.

† Hydrolysis of 2',3' cyclic phosphate.

‡ ATP-PP_i exchange.

§ Oligonucleotide circularization.

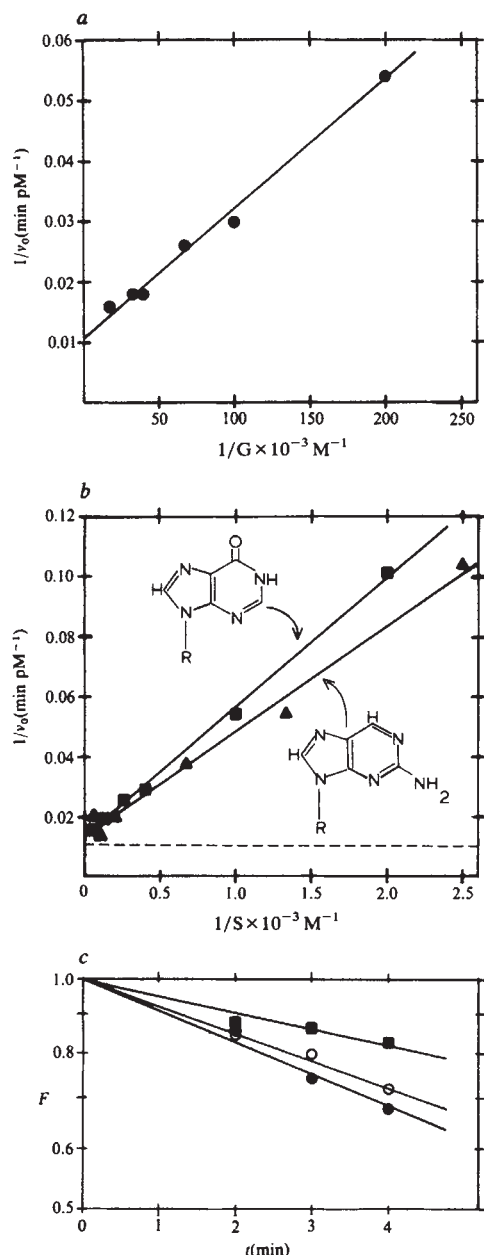


Fig. 4 Kinetics of splicing with (a) guanosine and (b) inosine (■) and 2 APr (▲) are expressed in the form of Lineweaver-Burk plots. $[\text{pre-rRNA}]_0 = 200 \text{ pM}$. The molecular structure of each analogue is shown. R, ribose. The graph for guanosine from a is extrapolated in b (dashed line). c, The velocity of $[\alpha\text{-}^{32}\text{P}]\text{G}$ -labelled IVS production is inhibited by inosine. ^3H -pre-rRNA was incubated in splicing conditions in the presence or absence of unlabelled inosine or adenosine. All reactions contained the same concentration of a labelled guanosine compound (guanosine + $[\alpha\text{-}^{32}\text{P}]\text{GTP}$ to give a total concentration of 0.005 mM). Splicing kinetics were analysed as in Figs 1b and 2b. ●, No additional nucleoside; ○, 3.5 mM adenosine; ■, 3.5 mM inosine.

catalysts that cleave or ligate RNA. Pre-rRNA splicing, like an enzyme-catalysed reaction, occurs at a far higher rate than the comparable non-enzymatic reaction, even at very low substrate concentrations. In fact, in the conditions at which the pre-rRNA and most protein enzymes are active (neutral pH and physiological temperatures) RNA is very stable. The rate of hydrolysis of a phosphodiester bond in RNA at neutral pH and 30°C is $5 \times 10^{-8} \text{ min}^{-1}$ (ref. 15). Based on this value, it should take 34 h at 30°C for half of a population of molecules the size of the *Tetrahymena* pre-rRNA to be cleaved once. Instead, the molecules complete two cleavages and two ligations with a $t_{1/2}$

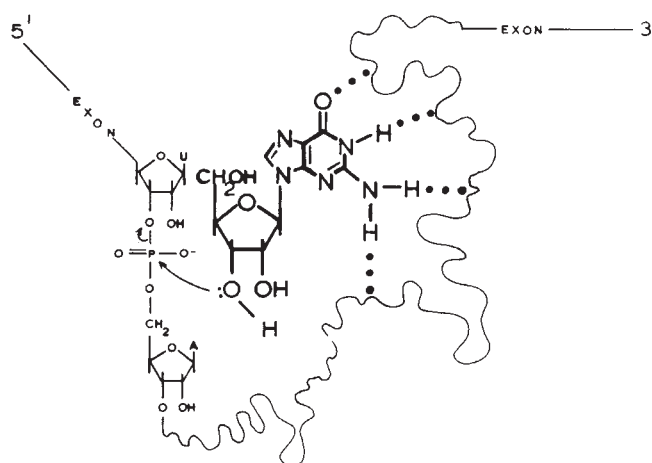


Fig. 5 A model for the nucleoside binding site on the pre-rRNA. The model is consistent with the kinetic and analogue data. The proposed hydrogen bonds (dotted lines) could involve one or two adjacent nucleotides of the RNA or, at the other extreme, four different nucleotides in very different regions of the RNA chain which are brought into close proximity by the RNA secondary and tertiary structure. In addition to the bases of the RNA, sugars and phosphates could be involved in hydrogen bonding. Also shown is a nucleophilic attack by the 3' oxygen at the phosphate of the 5' splice site. The resulting transesterification has been proposed to be the first step of the splicing reaction⁸⁻¹⁰.

of $1.33 \pm 0.38 \text{ min}$ at maximum velocity. The rate of RNA hydrolysis is comparable with that of self-catalysed splicing only at extremes of pH or temperature. For instance, at 27°C and pH 14, 1% of the bonds in an RNA molecule are cleaved in 0.7 min ¹⁶.

As dramatic as they seem, these comparisons of reaction rates actually understate the difference between chemical and self-catalysed cleavage of RNA. While chemical hydrolysis of RNA demonstrates some sequence preference, self-catalysed cleavage of the pre-rRNA occurs only at the splice sites. Moreover, self-catalysed cleavage does not occur by the normal mechanism for chemical cleavage: the former results in 5'-phosphate and 3'-hydroxyl termini, while the latter leaves the phosphate on the 3' terminus of the RNA.

Non-enzymatic ligation has been demonstrated when oligonucleotides with 5'-hydroxyl and 2',3'-cyclic phosphate termini are aligned head-to-tail on a complementary RNA template¹⁷. In this case a 2',5'-phosphodiester bond is preferentially formed. In the presence of the chemical catalyst ethylene diamine, the ligation occurs with a first order rate constant of about 10^{-4} min^{-1} , depending on the template used (S. A. Walstrum and D. A. Usher, manuscript in preparation). The pre-rRNA splicing reaction is 10^4 -fold faster than this ligation and specifically forms a 3',5'-phosphodiester bond. 3',5'-phosphodiester bonds have been observed in non-enzymatic reactions only when certain activated mononucleosides are used¹⁸.

Both the rate and the specificity of *Tetrahymena* pre-rRNA splicing make it appropriate and useful to consider the RNA a novel type of biological catalyst. We use 'catalyst' in the broad sense of a substance that accelerates the rate of a reaction. The *Tetrahymena* pre-rRNA differs from most enzyme catalysts, which are regenerated after each catalytic event and therefore serve as re-usable, *trans*-acting effectors of biological reactions. There are some enzymes, however, such as the type I restriction endonucleases^{19,20}, poly(ADP-ribose) synthetase^{21,22} and the transmethylase for *O*⁶-methylguanine²³, which are consumed in the reactions they catalyse. In the case of the pre-rRNA, a portion of the molecule is permanently changed as the splicing and cyclization reactions occur, but it is clear that the cleavage-ligation activity is not destroyed (A. Zaug, J. Kent, F. Sullivan and T.C., manuscripts in preparation).

The fundamental differences between RNA and protein as biological catalysts lie in other directions. RNA has a more limited potential as a catalyst because it has only four types of side chains, compared with the 20 of polypeptides. RNA does not contain residues like valine and phenylalanine which are entirely hydrophobic, nor does RNA have a residue like histidine that has the useful property of being ionizable near neutral pH. (An exception to this second generality has been found; *Escherichia coli* 5S rRNA undergoes a conformational change with accompanying release of a proton when the pH is increased from 7 to 8 (ref. 24).) Because of its hydrogen-bonding and base-stacking capabilities, RNA may be particularly well suited for the catalysis of reactions that involve nucleotides or polynucleotides.

RNA catalysts—ribozymes—can therefore be considered to be primordial enzymes, able to catalyse some reactions as well as proteins but having a much more limited potential as general biological catalysts. It has been suggested that RNA catalysts were common early in evolution and that nucleotide coenzymes might be vestiges of these early ribozymes^{25,26}. Whether or not this is the case, it seems unlikely that the *Tetrahymena* ribozyme is the only example of an RNA catalyst in present-day organisms.

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Splicing of fungal mitochondrial RNA appears to be largely an RNA-mediated reaction (reviewed in ref. 11). RNA may have a catalytic role in the reactions of RNase P and the other ribonucleoprotein enzymes. RNA is involved in the catalysis of protein synthesis on ribosomes²⁷, and may even be involved in the peptidyl transfer reaction. In these examples, the catalyst requires both RNA and protein components. It seems possible that the proteins have evolved to refine and tune the structure and activity of what are basically RNA machines²⁸.

After submission of this paper Altman, Pace and co-workers reported that the RNA component of RNase P is the catalytic subunit of the enzyme^{29,30}. In addition to providing another example of an RNA molecule that lowers the activation energy for a specific biochemical reaction, RNase P is the first proven example of an RNA molecule that catalyses a reaction without itself undergoing any net change.

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LETTERS TO NATURE

A burst emission mechanism for coherent radiation from pulsars

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Various mechanisms for generating coherent curvature radiation have been proposed¹ to explain the high brightness temperature of pulsars at radio frequencies. The bunching of counterstreaming charged particles^{2–5}, although requiring rather special conditions and subject to criticism⁶, has hitherto seemed the most plausible. Here we propose an entirely new mechanism of 'burst emission', which initiates at the surface of a neutron star and occurs naturally without any need to postulate special conditions. We argue that the induced electric field in the near magnetosphere of a rotating neutron star is sufficiently strong to detach moderately large grains of solid matter from the surface in the polar-cap regions. The detached grains erupt and form ascending plumes or jets of dense and highly charged

gas. These thread-like plumes, of length $h \geq 10^2$ cm, then accelerate along the open magnetic field lines and emit intense partially coherent radiation, at radio frequencies, with a low-frequency cutoff at c/h . Our estimates indicate that burst emission can account for the principal characteristics of the observed radiation from pulsars at radio frequencies.

In the pulsar models proposed by Sturrock² and by Ruderman and Sutherland⁵, cascade electron-pair production occurs due to the emission of curvature radiation. According to these models, outward-moving streams of particles tend to bunch, thus accounting for the coherent emission at radio frequencies. The condition for a pair-producing discharge in a magnetic field of $B = 10^{12}$ G, within a distance H from the surface, is

$$(\rho/R)P^3 < 2 \times 10^2 (H/R)^{1/2} \quad (1)$$

where ρ is the radius of curvature of the magnetic field lines, $P = 2\pi\Omega^{-1}$ the rotation period and R the radius of the neutron star. The inequality comes from the requirements: (1) H is less than the mean free path of pair-producing photons and (2) the potential difference across H is less than the model-independent maximum value

$$\phi = BR^3\Omega^2/c^2 = 1 \times 10^{13} P^{-2} V \quad (2)$$

for $R = 10^6$ cm. In the Ruderman–Sutherland model the gap thickness is small ($H < R$), and the right side of equation (1) is ~ 10 . To account for coherent radiation from pulsars of $P \sim 1$ s,

it is necessary to assume $\rho \sim R$ due to the presence of multipole field components. A possible objection is that multipole fields will have decayed in the slowest pulsars of greatest age. In the Sturrock model we have $H \sim R$, but now $\rho > R$ because the field is assumed to be dipolar, and again a cutoff exists at $P \sim 1$ s. A possible objection in this case is that bunching, and hence coherent emission, seems unlikely because the discharge now occurs over a large region of the magnetosphere.

The proposed burst emission mechanisms takes an entirely different approach in considering that coherent radiation at radio frequencies is a natural consequence of the emission process.

The lattice binding energy ϵ for iron atoms in a magnetic field $B \sim 10^{12}$ G has been found to be less than previously estimated⁷. The revised binding energy⁸ in linear atomic chains is 2.6 keV, with a lattice spacing $d = 5 \times 10^{-9}$ cm corresponding to a density $D = 5 \times 10^3$ g cm⁻³, and a melting point at a temperature $\sim 10^7$ K. An electric field $(4\pi\epsilon/d^3)^{1/2} = 2 \times 10^{11}$ V cm⁻¹ is thus sufficient to detach singly-charged ions from the surface of a neutron star, as suggested by Michel⁹ and also by Cheng and Ruderman¹⁰. The co-rotating electric field normal to the surface in the magnetic polar regions is $E = E_0\theta$, where $E_0 = B\Omega R/c$ and θ is a model-dependent parameter. Possibly θ is self-adjusting to ensure equality of the positive and negative currents emanating from different parts of the magnetic polar regions; θ may also have large fluctuations² on time scales R/c and $R_L/c = \Omega^{-1}$, where R_L is the light-cylinder radius. By following the practice of assuming $\theta = (R/R_L)^{1/2} = 1.4 \times 10^{-2} P^{-1/2}$, we obtain

$$E = 8 \times 10^8 P^{-3/2} \text{ V cm}^{-1} \quad (3)$$

for the conventional values $B = 10^{12}$ G and $R = 10^6$ cm. When $P > 4 \times 10^{-2}$ s, the surface electric field E is generally insufficient to detach singly charged atoms. (The Crab pulsar PSR0531 + 21, with period $P = 0.033$ s, is close to the critical value and may therefore need special consideration.)

The cohesive strength of most materials is considerably less than theoretical estimates, due to structural irregularities¹¹, and no doubt the crustal material of neutron stars shares this property with terrestrial matter. We propose that aggregates of atoms, or small pieces of solid matter, positively charged, are wrenched from the surface of the neutron star. (Sputtering caused by high-energy bombardment is an alternative possibility.)

Conceivably the surface is irregular on the microscopic scale; also it may be fractured by horizontal compressive or tensile forces, or pitted by previous burst emissions, thus facilitating the detachment of solid matter by an electric field. The crustal material may be non-uniformly cohesive, and have a granular structure caused by composition inhomogeneities and lattice defects. In any event, we assume that the electric field of equation (3) is generally sufficient to detach small grains from the surface layers in polar regions where the surface is positively charged.

A grain, as it detaches, remains in electrical contact with the surface via a bridge of tenuous gas, and therefore stays at roughly the same electrical potential as the surface. This causes electrons to discharge down the bridge, and the grain is disrupted owing to enhanced electrical stresses and converted into a dense, partly ionized plasma. We visualize the grain bursting from the surface as a narrow plume of gas that becomes highly charged as it ascends along the magnetic field lines. For an electrically conducting prolate hemispheroidal plume of height h and radius a , the internal electric field is

$$E_{\text{int}} = E - qh^{-2}\Lambda \quad (4)$$

where q is the total charge of the plume and $\Lambda \approx (\ln 2h/a - 1)$ for $h \gg a$. An internal electric field $E_{\text{int}} \ll E$ is sufficient to cause electrons to drain downward, creating a total positive charge of approximately

$$q = Eh^2\Lambda^{-1} \quad (5)$$

that increases with h^2 as the plume grows in height. If m is the

mass of the unipotential plume, the height increases until

$$q \rightarrow \alpha m, \quad \alpha = eZ/m_H A \quad (6)$$

and the constituent atoms (of atomic number Z and weight A) become fully ionized. Thus, a plume grows to a height

$$h = (\alpha m \Lambda / E)^{1/2} = 5 \times 10^4 m^{1/2} P^{3/4} \text{ cm} \quad (7)$$

from equations (5) and (6), for iron atoms, with $\Lambda = 50$. Hence, microgram plumes (corresponding to $a \sim 10^{-3}$ cm) erupt to a height $h \sim 10^2$ cm for $P \sim 1$ s. The plume in the form of a detached thread accelerates and ascends along the field lines at a speed approaching the speed of light. In this discussion we ignore the stretching of the thread due to differential acceleration.

If the surface of the neutron star is smooth, the outwardly directed force per unit area is $E^2/4\pi$. The electric force on a grain of surface area πa^2 exceeds the gravitational force when $a^2 > 4gm/E^2$, where $g = GM/R^2$; hence, from equation (7)

$$\frac{h}{a} < \left(\frac{\alpha \Lambda E}{4g} \right)^{1/2} = 6 \times 10^3 P^{-3/4} \quad (8)$$

for M equal to a solar mass. There are two reasons for supposing that this gravitational limit is not serious. First, it is unlikely that the surface is smooth on the small scale, as it is probably pitted by constant burst emission. The surface field strength will therefore vary, and at high spots have values considerably greater than E given by equation (3). (This is one of the reasons stated previously for supposing that grain detachment is plausible.) Second, during the burst emission process, electrons drain downward and heat the surface to a temperature $T > \epsilon/k \sim 10^7$ K, thus releasing additional gas that feeds the base of the plume. With a simple hydrodynamic model consisting of constant mass-flow input, we find that the plume cuts off at $h < h_{\text{max}}$ (corresponding to $h \sim c$), where

$$h_{\text{max}} \sim \frac{\alpha \Lambda m^{2/3} D^{1/3}}{2E} \left(\frac{\epsilon}{Am_H c^2} \right)^{1/2} = 3 \times 10^6 m^{2/3} P^{3/2} \text{ cm} \quad (9)$$

and thereafter becomes a space-charge limited ion beam that dwindles as the hot spot cools. Equation (7) satisfies equation (9) for microgram plumes at normal values of P . A detached grain of very small mass, according to this model, triggers a plume of much larger mass.

The positive and negative currents emanating from the magnetic polar regions have characteristic values²

$$J^\pm = \frac{c\phi}{4\pi} \quad (10)$$

where ϕ is given by equation (2). In this discussion we are interested only in the positive currents originating at both polar caps that are assumed to be responsible for the coherent emission at radio frequencies. (Negative currents are readily explained by the thermionic emission of electrons.) The energy attained by the positive charges is $\gamma mc^2 = q\phi$, where

$$\gamma = 4\pi\alpha J^+ / c^3 = 6 \times 10^3 P^{-2} \quad (11)$$

We note that the cyclotron radius $\sim \gamma mc^2 / qB_L$ at the light cylinder, where $B_L = B(R\Omega/c)^3$, equals the light-cylinder radius R_L , but we ignore the possibility of synchrotron radiation. The mass-loss rate due to burst emission

$$\dot{M} = \alpha^{-1} J^+ = 2 \times 10^{13} P^{-2} \text{ g yr}^{-1} \quad (12)$$

is clearly negligible for a neutron star.

The peak intensity of coherent curvature radiation from a point charge occurs at the critical frequency

$$\omega_c = \frac{3\gamma^3 c}{2\rho} = 1 \times 10^{14} P^{-13/2} \text{ s}^{-1} \quad (13)$$

if we assume a value $\rho = R\theta^{-1}$ for the radius of curvature of the magnetic field lines. The intensity emitted in the forward

axial direction by a line-charge q of length h , for $\omega < \omega_c$, is

$$I(\omega) \sim \frac{q^2 c}{\rho} \left(\frac{\omega \rho}{c} \right)^{1/3} \left(\frac{c}{\omega h} \right)^2 \sin^2 \left(\frac{\omega h}{c} \right) \quad (14)$$

When $\omega_c < c/h$, interference is negligible, and we obtain the usual result $I(\omega) \propto \omega^{1/3}$. Now consider the case when $\omega_c > c/h$. The peak intensity occurs at $\omega = c/h$, and has the value

$$I_{\max} \sim \frac{q^2 c}{\rho^{2/3} h^{1/3}} \quad (15)$$

which is proportional to $h^{10/3}$ for $q \propto h^2$. For $\omega < c/h$, we have $I(\omega) \propto \omega^{1/3}$; and for $\omega > c/h$, then $I(\omega) \propto \omega^{-5/3} h^{-2}$, and the radiation is only partially coherent.

Pulsars have spectral indexes¹² in the range -1 to -3 . For line-charges the spectral index is $-5/3$, with a low-frequency cutoff at c/h . If the line-charges have a length distribution $N(h) \propto h^{-\beta}$, the spectral index becomes $\beta - 14/3$. These estimates are only approximate, and ignore variation of the curvature of the field lines.

The energy radiated by each line-charge is of the order

$$\epsilon_r = \frac{q^2 \rho^{1/3}}{h^{4/3}} \quad (16)$$

and radiation reaction is unimportant provided $\epsilon_r < q\phi$, or $h < R\theta^2 \Lambda^{3/2} \sim 10^5 P^{-1} \text{ cm}$, which is amply satisfied for metre-length threads. The total coherent radiation from the thread-like charges is of the order $L = \epsilon_r q^{-1} J^\pm$, or

$$L = \frac{c\phi E}{4\pi\Lambda} (h^2 \rho)^{1/3} = 3 \times 10^{27} h^{2/3} P^{-10/3} \text{ erg s}^{-1} \quad (17)$$

for which the low-frequency cutoff is c/h . Most pulsars have observed beam luminosities¹ at radio frequencies in the range 10^{26} – $10^{30} \text{ erg s}^{-1}$, and our results are in reasonable agreement for $h \sim 10^2 \text{ cm}$, corresponding to microgram plumes.

The number of bursts or jets emitted each second in $\dot{N} = q^{-1} J^\pm$, or

$$N = \frac{cR\theta\Lambda}{4\pi h^2} = 2 \times 10^{15} h^{-2} P^{-1/2} \text{ s}^{-1} \quad (18)$$

and this rate is too large for individual bursts to be observed as micropulses. We note, however, that with $h \sim 3 \times 10^2 \text{ cm}$ and $P \sim 1 \text{ s}$, the statistical fluctuation $\delta N \sim N^{1/2}$ gives $\delta \dot{N} \sim 10^5 \text{ s}^{-1}$, consistent with a shot-noise interpretation¹³ of pulse micro-structure.

The proposed burst emission mechanism offers a natural explanation of the coherent radiation occurring predominantly at radio frequencies, and for the steepness of the observed spectra. Burst emission, or some variant of such emission, does not necessarily exclude the possibility of previously proposed mechanisms contributing to the observed complexity of pulse structures and their spectra. In this preliminary study we have concentrated on discussing the plausibility of a burst emission mechanism, and have ignored such matters as polarization (curvature radiation from line-charges is much the same as from bunches), optical and X-ray emissions (which are probably not coherent) and drifting subpulses.

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Magnetic pair production in Cygnus X-3 and a cut off in the γ -ray spectrum

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The binary system Cygnus X-3 is a source of high energy γ rays ($>10^{15} \text{ eV}$)^{1,2}, and the existence of quiescent radio emission from this system³ is suggestive of a strong magnetic field extending well beyond the binary orbit⁴. We show here that the high-energy γ rays traversing this field could be attenuated by magnetic pair production process, resulting in the rather sharp steepening of the γ -ray spectrum beyond about 10^{16} eV . Using the observed spectral steepening², we derive a magnetic field strength of 0.7 G in the region $\sim 10^{14} \text{ cm}$, where most of the observed radio emission takes place. The observed light curve above 10^{15} eV shows only one significant narrow peak at a phase of about 0.2 from the X-ray minimum. This could result from the magnetic bending of the charged particles from the pulsar before interacting with the enshrouded matter. We predict that the relative contribution of steady flux should increase beyond 10^{16} eV .

The Cygnus X-3 system consists of a pulsar in close orbit around a companion star. The companion star undergoes mass loss through a dense stellar wind. Such an outflow of gas was invoked to explain the profile of the X-ray modulation^{5,6}. Making use of the observed value of $\dot{P}/P$ and assuming that the outflow of gas is spherically symmetrical, Vestrand⁴ derived the density profile of the outgoing gas to be

$$n(R) = 3 \times 10^{13} R_{11}^{-2} \text{ cm}^{-3} \quad (1)$$

where R_{11} is the distance from the star measured in units of 10^{11} cm . From a detailed modelling of the binary system Ghosh *et al.*⁷ obtained the total mass M_T of the system to be $< 6 M_\odot$, and thus the binary orbit $a \approx 10^{11} (M_T)^{1/3} \approx 1.8 \times 10^{11} \text{ cm}$.

Quiescent radio emission has been observed³ in the frequency region 1.4 to 80 GHz , the spectrum being consistent with non-thermal radiation. The size of the radio source is approximately 10^{14} cm at 8 GHz (ref. 8). Because of energy loss, the electrons responsible for radio emission cannot be transported even up to 10^{13} cm . Therefore, it was postulated⁴ that the radiating electrons are supplied by the γ rays around 100 MeV . The azimuthal component of the magnetic field frozen in the stellar wind has the dependence $B_\perp(R) = B_{\perp 0} R_{11}^{-1}$, where $B_{\perp 0}$ is the field strength at 10^{11} cm . Using the density profile given by equation (1), it can be shown that the $B_{\perp 0}$ should be at least 10^2 G in order to avoid the Razin–Tsytoich effect⁹ at the observed frequencies. From the best fit to the radio data, a value of $1,330 \text{ G}$ has been obtained⁴ for $B_{\perp 0}$.

The observed integral γ -ray spectrum from Cygnus X-3 above a few hundred GeV ^{1,2,10–17} is shown in Fig. 1. Note that the flux values reported by different groups around the same energy region differ by a factor of ~ 2 . This could be due either to temporal variation of the source or to the uncertainty in energy estimation. The high-energy γ rays are attenuated by their interaction with the universal black-body photons^{2,18}. Therefore, we have chosen a differential spectrum of the type

$$j_\gamma(E) = 2.15 \times 10^{-9} E^{-1.7} \text{ photon cm}^{-2} \text{ s}^{-1} \text{ GeV}^{-1} \quad (2)$$

as the measure of the production spectrum of γ rays to calculate the effect of propagation in the magnetic field surrounding the binary system. The corresponding integral spectrum is shown as curve *a* in Fig. 1.

For the magnetic pair production process, the attenuation

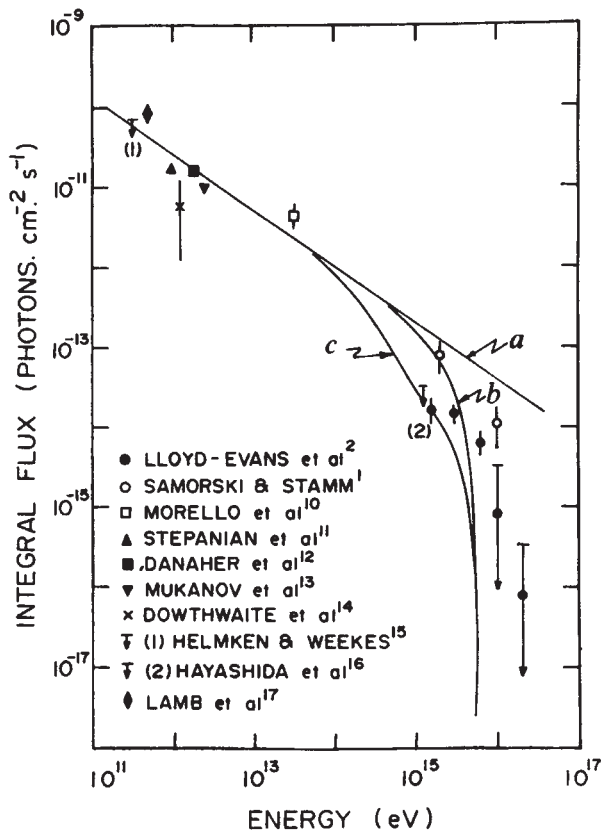


Fig. 1 Time-averaged integral flux values of γ rays above 10^{11} eV from Cygnus X-3. Curve *a* is the chosen production spectrum, *b* is the calculated spectrum after taking into account the attenuation due to magnetic pair production with a field strength $B_{\perp 0} = 1,330$ G and curve *c* is the attenuated spectrum after interaction with the universal black-body photons en route.

coefficient for γ rays is given by¹⁹

$$k = \frac{1}{2} \frac{\alpha B_{\perp}}{\lambda_e B_c} T(\chi) \text{ cm}^{-1} \quad (3)$$

Here α is the fine structure constant, λ_e the Compton wavelength, $B_c = m^2 c^3 / eh$ the critical magnetic field, $\chi = \frac{1}{2} (h\nu B_{\perp} / mc^2 B_c)$ and $T(\chi) = 0.16 \chi^{-1} K_{1/3}^2(2/3\chi)$. For small values of χ , $T(\chi)$ can be approximated as $0.46 \exp(-4/3\chi)$. It is clear that the attenuation coefficient increases exponentially with energy, reaches a constant value and then decreases slowly as $\chi^{-1/3}$. The attenuated γ -ray spectrum from Cygnus X-3 would then be

$$j_{\gamma}(E) f_B(E) \exp \left[- \int_{x'}^{\infty} \left\{ 2.14 \times 10^{-6} B_{\perp}(R) T(\chi) + \frac{n(R)}{L} \right\} dx \right] \quad (4)$$

where x is the distance from the pulsar along the line of sight, $L = 88 \text{ g cm}^{-2}$ is the attenuation length for pair production in the gas, $R = \sqrt{a^2 + x^2 - 2ax \cos \theta}$ and θ is the phase angle relative to X-ray minimum. Assuming that the γ rays are produced in the atmosphere of the companion star, the integration in equation (4) was carried out from $x' = a \cos \theta$. The value of θ corresponds to the phase of the γ -ray peak relative to the X-ray minimum. The Kiel group¹ observed this peak at a phase of 0.15, while the Haverah Park results² indicate this at 0.25, and hence a value of 0.2 was chosen for our calculations. The term $f_B(E)$ in equation (4) is the attenuation factor resulting from the interaction of γ rays with the universal black-body photons along the line of sight. To evaluate this term we have

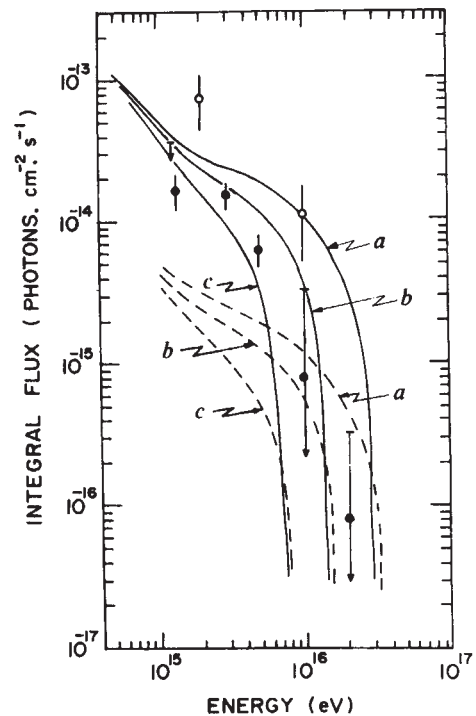


Fig. 2 Observed integral spectrum of γ rays from Cygnus X-3 above 10^{15} eV; the symbols used here are as in Fig. 1. The solid curves are the calculated spectra for different values of $B_{\perp 0}$ indicated. The dashed curves are the mean spectra during the phase, when the pulsar is in front of the companion star, for different values of $B_{\perp 0}$ as in the case of the solid curves; these spectra are normalized to 10% of the flux value (solid curve) at 10^{15} eV. All the calculated curves include the effect of the interaction with the universal black-body photons. $B_{\perp 0}$ values: *a*, 250 G; *b*, 500 G; *c*, 1,000 G.

used the cross-section given by Gould and Shreder²⁰ and a value of 12 kpc for the distance of Cygnus X-3²¹.

Curve *b* in Fig. 1 is the calculated integral spectrum without the term $f_B(E)$, using the best-fit value of $B_{\perp 0} = 1,330$ G, derived from the quiescent radio spectrum. Curve *c* is the calculated spectrum after taking into account the attenuation of γ rays by black-body photons. These spectra nearly cut off beyond about 2×10^{15} eV: our calculations show that a change in the production spectrum only alters the flux values below 2×10^{15} eV and the near-cut off beyond this energy is dependent only on the assumed magnetic field. The observation of a finite flux of γ rays above 2×10^{15} eV shows that the field strength used here is large. Therefore, we have tried different values of $B_{\perp 0}$ to obtain a better fit to the high energy γ -ray data.

The calculated γ -ray spectra are shown in Fig. 2, along with the observed flux values above 10^{15} eV. The solid curves *a*, *b* and *c* correspond to $B_{\perp 0}$ values of 250, 500 and 1,000 G respectively. The observed steepening rules out a magnetic field as low as 250 G. The most probable value of $B_{\perp 0}$ is about 700 G, which corresponds to a field strength of about 0.7 G at 10^{14} cm, the region around which most of the observed radio emission takes place.

The Cygnus X-3 pulsar is believed to be responsible for the acceleration of ions²² up to energies $\geq 10^{16}$ eV. These ions interact with the gas surrounding the companion star to produce γ rays through the decay of π^0 mesons²³. If this hypothesis is correct, γ rays should also be produced when the pulsar comes in front of the companion star, through interactions of accelerated ions with stellar wind material. The γ -ray spectrum thus produced is proportional to

$$j_{\gamma}(E)f_B(E) \int_0^{\infty} \exp\left[-\int_0^x \frac{n(R) dx}{\Lambda}\right] \left[\frac{n(R) dx}{\lambda}\right] \times \exp\left[-\int_x^{\infty} \left\{2.14 \times 10^{-6} B_{\perp}(R) T(\chi) + \frac{n(R)}{L}\right\} dx\right] \quad (5)$$

Here, the first exponential term relates to the attenuation of ions, the second term to the interaction probability and the last exponential term to the attenuation of γ rays through pair production. The values of Λ and λ are taken as 67 and 50 g cm⁻² respectively.

Evaluating equation (5), we find that the γ -ray flux decreases by about 40% from phase 0.25 to 0.5 at energies where magnetic pair production is insignificant. When magnetic pair production dominates, the γ -ray flux increases with phase. Since the exact magnitude of this modulation depends on the influence of magnetic field on the charged particles before interaction, we do not consider this aspect here. Instead, we have averaged the flux over the entire phase when the pulsar is in front of the companion star. From the phase diagram¹, we obtain an upper limit of about 15% for the γ -ray flux outside the peaks at energies $>2 \times 10^{15}$ eV. We have normalized the mean integral spectrum to 10% of the integral flux, as determined from equation (4) at around 10^{15} eV. The integral spectra thus obtained with various values of B_{10} are shown in Fig. 2 as dashed curves. The results shown in Fig. 2 suggest that although the contribution from this near-steady component increases beyond 10^{16} eV, this component does not extend far beyond this energy. Thus the observed spectral steepening does not necessarily imply possible termination of the accelerated spectrum—the accelerated spectrum of ions may in fact extend beyond about 10^{17} eV.

The radius of curvature of a 10^{16} -eV proton in the magnetic field surrounding the star is of the same order as the radius of the star. It is quite reasonable to expect, depending on the structure of the magnetic field, that the ion would be deflected either into or out of the atmosphere, when the pulsar emerges from behind the star. This may explain the near absence of a second peak about the X-ray minimum. In addition, the spectral shape of γ rays between 10^{12} eV and 10^{15} eV is much flatter than that below 10^{12} eV. This apparent flattening of the spectrum could result from the following reason. As the energy decreases, the radius of curvature of the interacting particle decreases. This reduces the available path length along the line of sight in the enshrouded gas, for the production of γ rays. As a result, the flux at 10^{12} eV would be suppressed. The low-energy γ rays ≤ 100 MeV come directly from the pulsar and appear to have a different spectral slope. It will be interesting to look for the energy region at which these two spectra join.

Radiofrequency emissions observed during macroscopic hypervelocity impact experiments

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Banded low-frequency radiofrequency (r.f.) signals, very low frequency propagation and light emission have been recorded to precede, accompany and follow some large earthquakes¹⁻³, and mechanisms to account for these phenomena have been suggested recently^{4,5}, discussed briefly by Chi-Yu King (ref. 6 and references therein) and summarized by Sadovski⁷. Banded r.f. emission has also been detected in a series of laboratory tests in which samples of granite and other hard rocks were fractured under static pressure⁸. Here we report observations of banded r.f. emission generated during and after macroscopic hypervelocity impacts of small projectiles on hard rocks. We believe that our results may help to further the understanding of earthquake emissions and the mechanism of impact magnetization⁹, both of which are associated with the fracturing of rocks under some kind of stress.

Observations were made during a series of experiments devoted primarily to the study of mechanical and magnetic effects associated with hypervelocity cratering¹⁰. The apparatus used in our tests is described elsewhere¹⁰, and illustrated schematically in Fig. 1. Modified explosive shaped charges¹¹ were used to accelerate small aluminium projectiles (~ 1 g) up to velocities of ~ 10 km s⁻¹ against hard targets. The targets consisted of leucite blocks, $40 \times 40 \times 35$ cm, and $50 \times 50 \times 40$ cm blocks of 'artificial' rock, obtained by mixing, in the ratio 1:2 by volume, alumina concrete and marble powder. Both types of targets were encased in strong dural boxes.

In most of the 21 tests performed to date, the r.f. receiver system consisted of several coils (loop antennae), typically two or three for each test, orientated so as to allow the simultaneous detection of various components of any transient magnetic field (vertical, radial and/or azimuthal). Each loop antenna consisted of a 50-turn coil of 10-cm diameter. In the last four tests, we used Rogovski (toroidal) coils (500 turns of 1-cm diameter over a loop of 20-cm diameter) to obtain a 'clean' signal for the

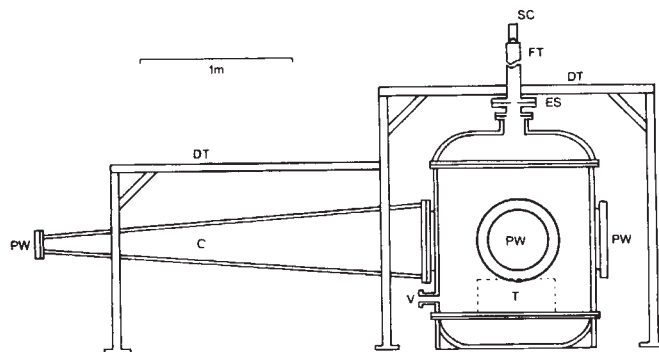


Fig. 1 The target vacuum chamber. The drawing is to scale, except stainless steel. SC, explosive shaped charge; FT, flight tube; DT, deflection table; ES, explosively operated shutter; PW, perspex windows; C, conical extension to the vacuum chamber, which brings the viewing window out of the depth of field of the IMACON camera; T, target; V, to the vacuum pump and manometers.

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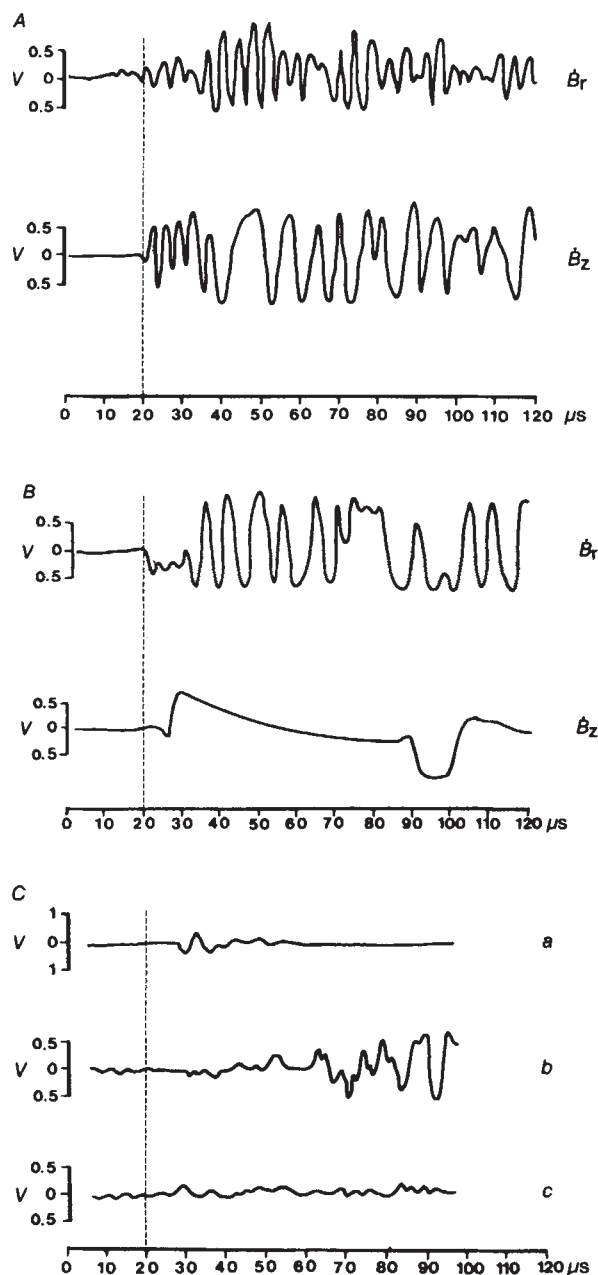


Fig. 2 *A*, Impact in air at atmospheric pressure. *B*, Impact in *vacuo* (~1 torr residual pressure). The target in *A* and *B* is leucitite. The vertical scales are 1 V peak-to-peak. The vertical broken line indicates the moment of impact. *C*, Impact in *vacuo*; the target is a block of 'artificial rock'. Signal *a* is from the Rogovski coil, signal *b* from the unscreened radial coil and *c* from a mechanically screened radial coil. Note the different vertical scales.

azimuthal component of the transient magnetic field. An IMACON 790 fast framing camera (frame rate 10^5 s^{-1}) allowed the pre-impact velocity of the projectile to be measured with an accuracy of ~2%, and allowed us to follow the development of the cratering events, the formation of the ejecta and the expansion of the plasma cloud produced by the impact. Of the 21 tests, seven were performed in air at atmospheric pressure, and the rest in the vacuum chamber shown in Fig. 1, at a residual pressure varying between 6 and 0.1 torr. The output signals from the coils were recorded, via buffer amplifiers, on a multi-channel SE 7000 tape recorder having a bandwidth of 300 kHz. Measurements performed using a storage scope during the first series of tests showed that this bandwidth was adequate, as no

large-amplitude signal having a frequency higher than a few hundred kHz was detected.

Figure 2A shows the vertical (*z*) and radial (*r*) components of the transient magnetic field in a typical test performed in air at atmospheric pressure. The coil measuring the *z*-component was placed on the target surface surrounding the impact point, while the coil measuring the radial component was placed vertically ~12 cm from the impact point. The positions of the coils were important when considering the onset time of the signals, as this time could yield a clue to the mechanism responsible for the generation of the observed r.f. For the tests performed in air, the frequency of the oscillations was in the range 100–200 kHz. A typical result for the tests performed in *vacuo* is shown in Fig. 2B; the frequency of the radial component is somewhat lower, although still of the same order, while the behaviour of the vertical component is completely different and appears as an almost rectangular pulse which decays slowly. This behaviour has been discussed elsewhere⁹ and has been used to give experimental support to the theory of impact magnetization proposed by P.C. and G.M.¹²

The values of the recorded frequencies vary from test to test, but generally they are of the same order of magnitude irrespective of ambient gas pressure or target material. Those shown in Fig. 2A and B are quite typical, although in some cases values as low as 100 kHz have been recorded for the tests in *vacuo*. Figure 2C shows the signal recorded from the Rogovski coil during a test performed in *vacuo* on an artificial rock target (*a*), together with the signal from two radial coils, one unscreened (*b*) and one mechanically screened by a 2-mm plastic sheet (*c*). Note that in the latter case the r.f. signal was much smaller.

The frequencies detected are too low (~100 kHz) to have been generated in the impact-produced plasma by an oscillating dipole type of mechanism, as the dimensions of the current-carrying plasma are too small (20–50 cm, say). Also, they cannot have been generated by the conversion of electron plasma waves into electromagnetic waves for two reasons. First, electron plasma waves are strongly density-dependent, but in our experiment while the plasma diffuses and becomes more tenuous by three or four orders of magnitude over the period of observation, the frequency of the observed oscillations does not vary much over the same period. Second, from estimates of the plasma electron density, the plasma frequency is found to be of the order of several GHz even during the latest stages of observations. On the other hand, the frequencies observed in our experiments are comparable with those observed in association with some strong earthquakes^{1,2}. This suggests that if these observations can be ascribed to the same source as ours, the mechanism of r.f. emission is, up to a point, scale-independent. Finally, the tests performed with the screened and unscreened coils show that the recorded signals appear to be associated with the presence of the plasma near the coils, indicating that a mechanism other than direct electromagnetic wave radiation should be sought.

Our tests, both in air and in *vacuo*, were performed using interstitially dry rocks. Thus, a mechanism similar to that suggested by Lockner *et al.*⁴ to explain the emission of light during earthquakes cannot be used to account for r.f. emission during cratering, as these authors suggest that the vaporization of water in water-saturated rocks accounts for a change in electrical conductivity responsible for a significant charge separation. Cutolo⁵ invokes a very large oscillator (tens of kilometres) to account for the low frequencies observed during earthquakes. Our results render superfluous, although in principle do not invalidate, the mechanism proposed by this author, since the volume in which the observed r.f. signals were generated had, in our experiments, typical linear dimensions of tens of centimetres.

Alternative effects, based on the local (as opposed to large-scale) properties of the impact-perturbed area are now under investigation¹³, together with possible mechanisms coupling non-electromagnetic oscillations to electromagnetic radiation.

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Shapes of asteroids compared with fragments from hypervelocity impact experiments

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Light-curve observations have shown that most asteroids are non-axially symmetrical in shape, probably as a result of fragmentation undergone by objects with negligible gravitational binding¹. Some earlier laboratory simulations of catastrophic collisions at velocities not exceeding 4 km s^{-1} (refs 2–4) against cubic and parallelepipedal targets showed that the fragment shapes have a nearly gaussian distribution around the mean value of the axes' ratio $2:\sqrt{2}:1$. We report here results from hypervelocity experiments performed at $\sim 10 \text{ km s}^{-1}$ against free-falling bodies. We found that, regardless of the very different experimental conditions, the shape distribution obtained is closely similar to that obtained^{2–4} using targets of different shapes and materials and in good agreement with that of the main-belt asteroids of diameter smaller than $\sim 100 \text{ km}$. This distribution is not consistent with either the symmetrical shapes of the gravity-dominated asteroids, or the elongated Apollo-Amor objects.

In our experiments, aluminium projectiles weighing $\sim 1 \text{ g}$ were accelerated to velocities of $\sim 10 \text{ km s}^{-1}$ by means of a modified shaped charge technique, described in detail elsewhere^{5,6}. The velocity was measured to within 2% in each test by measuring successive positions of the projectile before impact using an Imacon 790 camera operating at a framing rate of 10^5 frames per s. The targets were made of fused alumina cement mixed with marble powder in the ratio 1:2 by volume, and moulded in the shape of triaxial ellipsoids with principal axes 30, 21 and 15 cm. With regard to cohesive strength, this material is very similar to several terrestrial rocks (for example, stronger than some granites but weaker than many basalts) and falls in the middle of many meteoritic materials. One reason for choosing this particular composition was to avoid the heterogeneity and anisotropy inherent in most natural rocks. The typical size of a

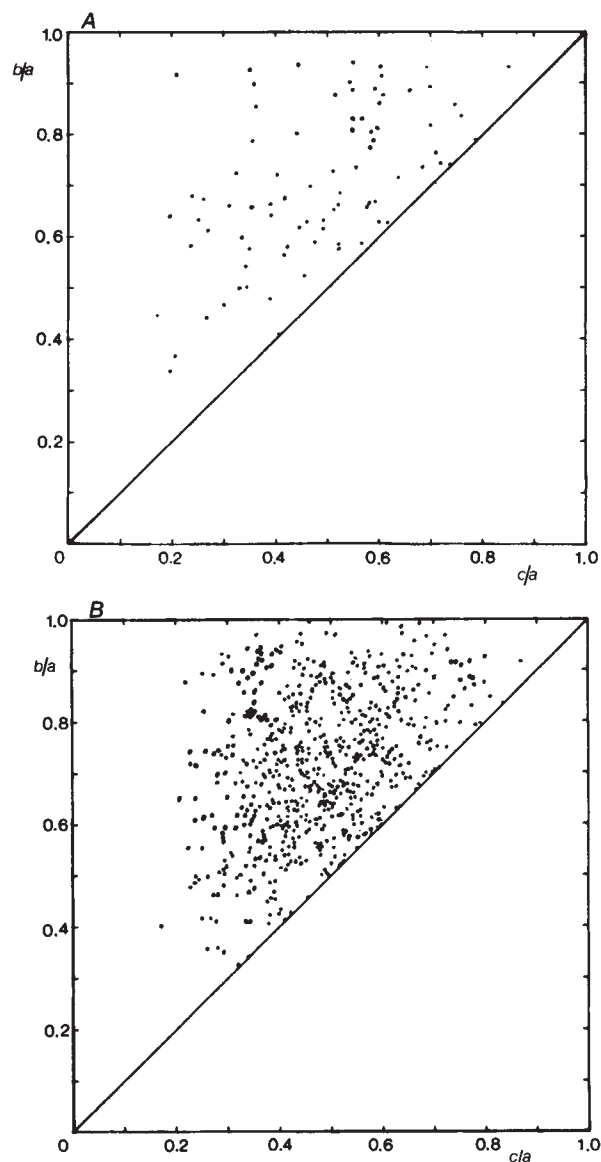


Fig. 1 Shape distribution of the fragments produced in two different experiments. A, Aluminium projectile $\sim 1 \text{ g}$, impact velocity 9.4 km s^{-1} , 85 fragments; B, aluminium projectile $\sim 1 \text{ g}$, impact velocity 9.8 km s^{-1} , 676 fragments.

grain of marble powder is only a few micrometres and the marble is chemically bound to the concrete.

The targets were placed in a chamber of 1 m^3 , evacuated to a pressure of <1 torr, and impacted vertically while free falling. The mass of the targets was of the order of 10 kg and that of the projectiles, measured using soft X-ray flash photography (duration of the pulse 30 ns), was of the order of 1 g . The specific energy of impact was $4\text{--}5 \times 10^7 \text{ erg g}^{-1}$, similar to that used by other investigators^{2–4}. Every fragment having a dimension larger than 15 mm was individually weighed to an accuracy of 10 mg , and the three axes a , b , c , defined as the maximum dimensions of the fragments in three orthogonal planes, were measured with a slide caliper to an accuracy of $\pm 0.02 \text{ mm}$ (see ref. 7 for further details of these experiments).

Interpretation of any impact experiment must take into account the complex problem of dimensional scaling. A critical discussion of this problem is given in ref. 1 where it is shown that, for fragmentation experiments, scaling is achieved by keeping the specific energy constant. This we have done, and thus we assume that our results are representative of a catastrophic collision and can be compared with those obtained by other authors.

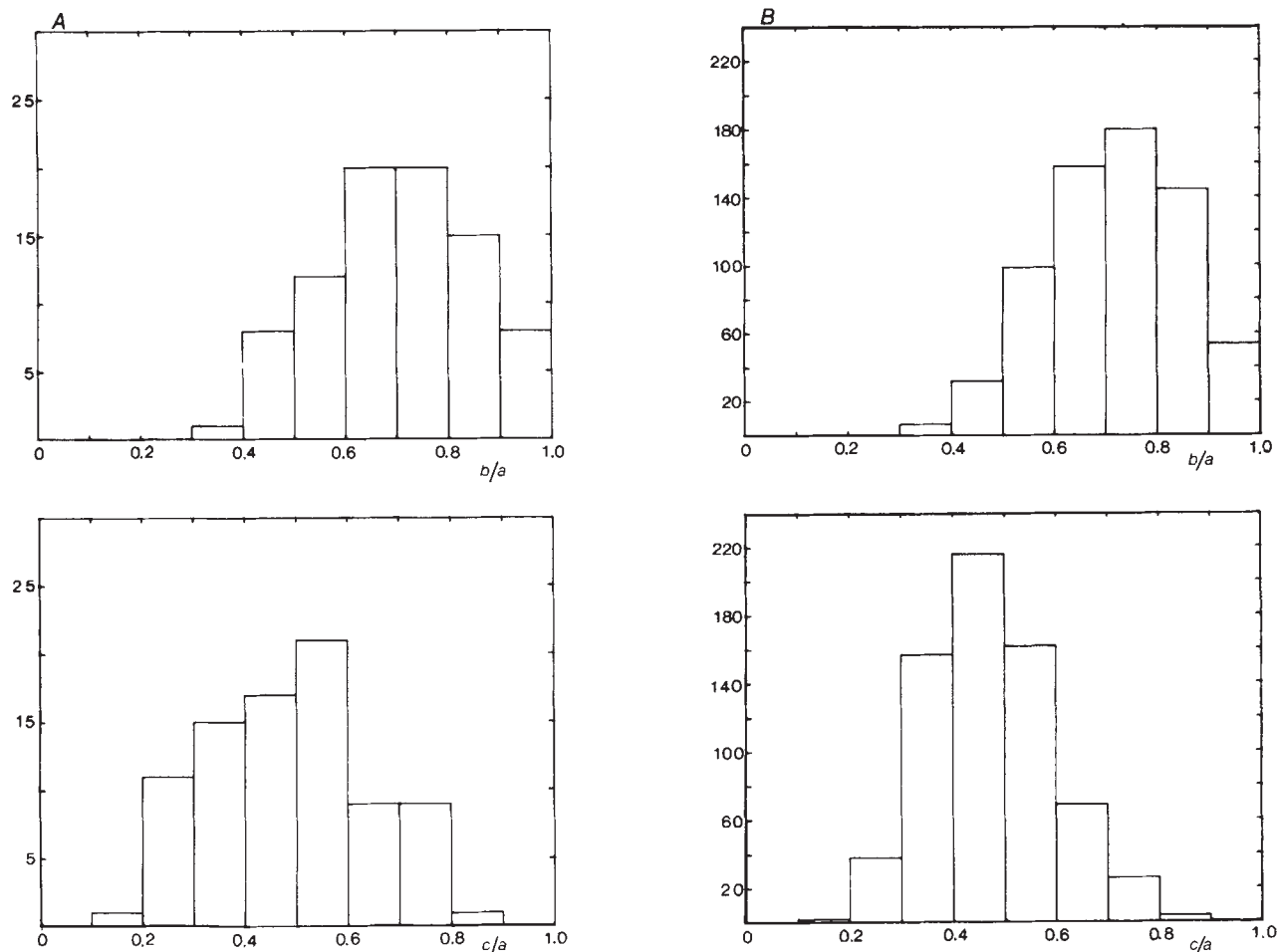


Fig. 2 A, Histogram for b/a and c/a corresponding to Fig. 1A; mean values are 0.49 and 0.72, respectively. B, Histogram for b/a and c/a corresponding to Fig. 1B; mean values are 0.48 and 0.72, respectively.

We have found that most fragments are characterized by moderately irregular shapes, and only a few objects have a high sphericity. Figure 1A and B show the plots of the axial ratios b/a and c/a for two typical experiments. We note that almost all the points lie in the region of the plane defined by $c/a > 0.2$ and $b/a > 0.3$. Only a very few points, corresponding to highly elongated or disk-shaped objects, are found outside this region. The mean value of the sphericity index, defined as $(bc/a^2)^{1/3}$, averaged over all the fragments from each experiment was found to be 0.70, as compared with 0.707 for a perfect triaxial ellipsoid with axial ratios 2:√2:1. The results are very similar to those found previously²⁻⁴ using a variety of target compositions and a wide spread of impact velocities not exceeding 4 km s⁻¹. Figure 2 shows the histograms of b/a and c/a for the two experiments. They fit normal distributions, centred around the mean values of 0.72 and 0.49 in one case, and 0.72 and 0.48 in the other, with values of σ of 0.12 and 0.16 (the values of b/a and c/a , for an ellipsoid with axial ratios 2:√2:1, are 0.707 and 0.5). We have verified that the shape distribution is independent of the size of the fragments. In fact, no systematic trend appears when b/a and c/a are plotted separately for different size ranges⁷.

Combining our results with those reported by Fujiwara *et al.*², we conclude that, as long as the impact specific energy remains within the limits associated with partial fragmentation, the shape distribution of the fragments remains unaffected by substantial changes in target composition, mass and shape, or by the mass and velocity of the impacting body (recall, for example, that Fujiwara *et al.*² used cubic targets of basalt and polycarbonate projectiles in some of their experiments). The ratio of the two terms √2 and 1 is strongly reminiscent of the ratio of the speeds of compressive and shear waves in materials

with low Poisson ratio such as granite (0.1–0.2) and the mixture used to make our targets (~0.15). On the other hand, the simple ratio 2:√2:1 could be a general statistical property of collision-generated fragments.

Having confirmed that our results and those of Fujiwara *et al.*² yielded a similar distribution of aspect ratios, we endeavoured to check whether the property mentioned above is a consequence of the (supposedly) random character of the fragmentation process. To this end, we simulated random fragmentation by a simple numerical experiment, in which a cube was cut by three sets of randomly spaced planes, each set perpendicular to one of the axes of the cube. The mean values of c/a and b/a for the resulting parallelepipedal pieces were found to be 0.26 and 0.49, respectively, with very broad distributions. No simple modification of this 'random cutting' process (such as imposing a lower cutoff to the axial ratios, or cutting the 'heaviest' slice at each step) could reproduce the experimental shape distribution satisfactorily. Thus, some as yet unidentified physical effect must be operating, and we believe that its nature and role deserve further investigation.

The shape distribution obtained from our experiments can be compared with that deduced from the light curves of the asteroids, bearing in mind that several asteroids have been observed at one opposition only. It should also be recalled that the b/a values deduced from the light curve amplitudes can be higher than those which can be derived only from observations at equatorial views. A first group of objects is formed by asteroids commonly believed to be fragments generated in a catastrophic collision. This is a set of 194 main-belt asteroids, with diameters ≤100 km. The mean value of b/a derived from the observed amplitudes is 0.77 ($\sigma=0.11$), and although this is increased by observation at not-equatorial views, it agrees

well with the shape distribution of laboratory fragments. This strongly supports the hypothesis that the small main-belt asteroids are of collisional origin⁸. On the other hand, if we consider the 29 main-belt asteroids with diameters >200 km, the equatorial amplitude of which can be estimated reliably from observations at several oppositions, we obtain an average value for b/a of 0.85 ($\sigma = 0.10$). The shape of these asteroids is therefore more symmetrical about the polar axis than that of collisional fragments. In the case of the larger asteroids, we expect that self-gravitational effects are relevant, especially if these asteroids are 'disrupted-and-reaccumulated' bodies with a 'rubber-pile' internal structure. In this case the gravitational forces should smooth out any large-scale irregularities.

We consider finally the set of 21 Apollo-Amor asteroids with known rotational properties. These are objects with typical dimensions of ~ 1 km, and orbits crossing those of the inner planets. They could be either extinct cometary nuclei or small collisional fragments ejected from the main belt by some peculiar dynamical mechanism⁹. Their mean value of b/a is 0.54 ($\sigma = 0.28$). This implies that among them very elongated and cigar-like shapes must be rather common. For example, 5 of the 21 Apollo-Amor objects have $b/a = 0.40$ while, by contrast, only 1% of the laboratory fragments exhibit such a low value for this ratio. The diameters of these asteroids are proportionally much smaller than those measured in the laboratory with respect to that of the parent body, so that a comparison between the two shape distributions is probably not fully meaningful. More experimental evidence is needed in the range of fine-grained debris to establish the genetic mechanism responsible for the shapes of the Apollo-Amor objects.

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Chaos in the non-stirred Belousov-Zhabotinsky reaction is induced by interaction of waves and stationary dissipative structures

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Order-disorder transitions are among the most important aspects of the problem of self-organization¹. The Belousov-Zhabotinsky (B-Z) reaction is a convenient model for studying these transitions because it displays not only a variety of regular wave patterns but also chemical turbulence. Chaos in this reaction is usually thought to be a local property², corresponding to a strange attractor in ordinary differential equations. In an active system, however, a different type of chaos (autowave chaos) may occur, which is not based on local mechanisms^{3,4}. We have now found that this type of chaos develops from the interaction of propagating waves and stationary dissipative structures. This interaction initiates a chain reaction of spiral wave production resulting in a reduction of the characteristic scales of the wave pattern and in the occurrence of chaos. If the physical conditions are inappropriate for the formation of dissipative structures, then no chemical turbulence occurs and the wave pattern remains regular. Therefore, chaos appears in the reaction as a result of structure formation.

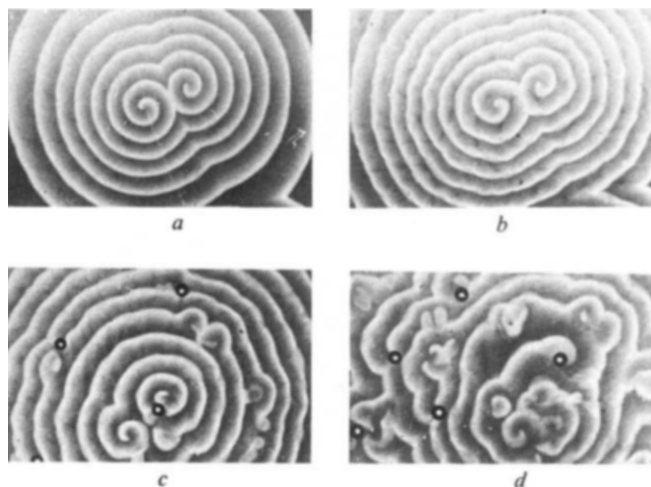


Fig. 1 Transition to chaos in the non-stirred B-Z reaction. *a-d*, Photos taken 5, 6, 10 and 11 min, respectively, after mixing the reagents.

The experiments were carried out in non-stirred B-Z reaction solution in a Petri dish 9 cm in diameter. The composition of the medium was similar to that commonly used^{5,6}: 0.1 M $\text{CHBr}(\text{COOH})_2$, 0.45 M H_2SO_4 , 0.3 M NaBrO_3 , 0.13 M $\text{CH}_2(\text{COOH})_2$, 5 mM ferroin. The Petri dish was mounted on a transparent substage kept at $20 \pm 0.2^\circ\text{C}$. In these conditions the medium exhibited excitable kinetics. A wave was induced by touching the solution surface with a silver wire, and the wavefront was then mechanically broken⁵ to produce a spiral wave which served as a source of periodic waves during the experiment. The waves were photographed under illumination with a flashlight. In such a reaction solution a regular wave pattern could be seen immediately after its preparation (Fig. 1*a*). However, after 3-5 min the regular order of wave propagation was broken (similar to refs 7, 8). The waves assumed an unusual sinusoid-like form (Fig. 1*b*), and the original smoothness of the wavefronts became distorted by the appearance of notches. The notches grew in size until wave-breaks occurred. These wave-breaks curled into rotating spirals (Fig. 1*c*) according to the well-known mechanism^{5,9}. Reproduction of the spiral waves continued (Fig. 1*d*) until the whole medium was filled with their small fragments and a small-scale turbulence developed.

These observations are consistent with the previously proposed³ theoretical scheme of spiral wave reproduction in an active medium by which waves can break in a non-homogeneous active medium (Fig. 2). The wave-breaks curl into rotating vortices (reverberators) which also become sources of waves. The waves produced by them, in turn, break at inhomogeneities, thus triggering the chain reaction of spiral wave reproduction. As a result, the medium fills with fragments of spiral waves and the regular wave pattern changes to a chaotic one.

Note that the scheme is applicable only in the case of a non-homogeneous medium. It can adequately explain, for example, the chaotic regimes in the heart (fibrillation), as the cells in heart muscle are not quite identical. However, it is clear

Table 1 Minimal thickness of the Belousov-Zhabotinsky reagent with which the hexagonal structures develop

KBr concentration (M)	Minimal thickness (mm)
0	1.26 ± 0.03
0.1	1.09 ± 0.03
0.15	0.85 ± 0.05
0.18	0.71 ± 0.03

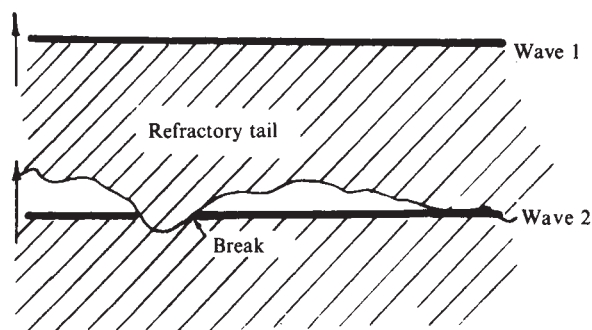


Fig. 2 Wave-break initiation in a heterogeneous medium. Waves propagate upwards, refractory (inexcitable) regions are hatched.

that the scheme cannot be directly applied to the B-Z reagent, which is a homogeneous solution.

Several hypotheses have been proposed to explain the mechanism of chaos in the non-stirred B-Z reaction. They are based on the over-critical fluctuations of concentrations large enough to produce a wave-break or a transverse instability of the wavefront¹⁰. We cannot exclude the possibility that these mechanisms are of significance in some extraordinary conditions. However, we have found experimentally a much more realistic one—whenever chaos occurred in a distributed system, it was always preceded by the appearance of stationary dissipative structures of a Benard cell type.

In some conditions the cells were clearly seen⁹, in others the cell boundaries remained practically invisible, giving the impression that chaos developed in homogeneous conditions. For example, the stationary cells were seen in a system with 4-cyclohexen-1,2 dicarboxylic acid¹¹ or bromacetone⁹ but they were almost invisible in malonic acid reagent. The reason for the difference is that in the first case the cell interior was blue (the oxidized form of ferroin), while the edge was orange (the reduced form of ferroin) due to an increased bromide concentration¹¹. In the second case, no spontaneous redox transition took place and therefore both the cell edge and the interior remained orange. The colour of the interior was only slightly less intense, and the general hexagonal pattern was hard to distinguish. However, the cells became clearly detectable again when the oxidation wave started propagating through them⁸ (the redox transition is limited at the cell boundaries and, because of this, the cells are easily seen during wave propagation due to a reduced intensity of the colour).

To verify the existence of a correlation between chaos and the dissipative structures, we performed experiments in which the chemical and physical characteristics of the system were varied in order to control the appearance of these structures. The Benard type cells are known to appear in a layer of liquid if its thickness exceeds a certain critical level. We therefore tried to obtain chaotic regimes in a tilted Petri dish. As expected, the cells appeared only in the deep part of the reagent (Fig. 3) and it was in this part that a chaotic regime could be observed. In contrast, a regular wave pattern was seen where the cells were absent.

The critical depth sufficient for the cells to appear could be reduced by increasing the initial concentration of KBr (Table 1). However, whatever its value, the boundary separating chaos from the regular wave pattern coincided in all cases with that of the region in which the cells occurred.

The effect persisted when the other reagent concentrations were altered within the following range: 0.15–0.60 M H₂SO₄, 0.1–0.3 M NaBrO₃, 0.05–0.4 M CH₂(COOH)₂, 1.5–5.0 mM

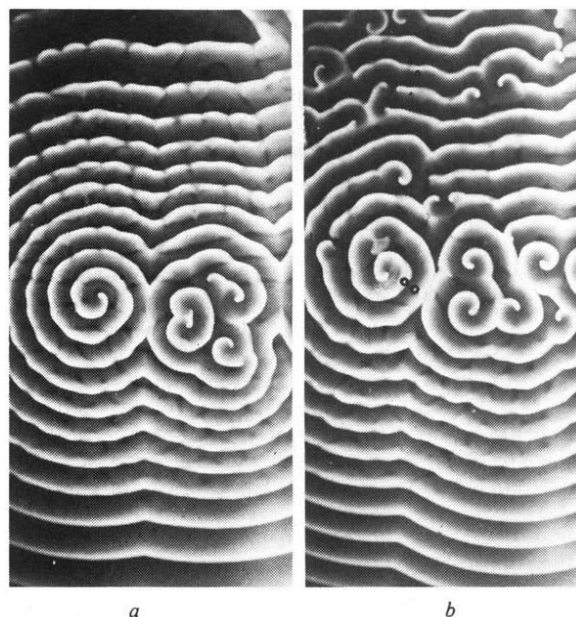


Fig. 3 Interaction of the propagating waves with the stationary cells leading to the reproduction of spiral waves. Photos were taken at 5-min intervals. At the centre of the dish a few spirals were initially induced (a) which served as wave sources during the experiment. The Petri dish was tilted, and the emerging spiral waves are seen only at the top of b, where the depth of the layer exceeded a critical value.

ferroin, that is, within the whole range of concentration values in which the propagating waves were observed.

The formation of cells could be prevented, even with the solution depth above its critical value (up to 3 mm), by covering the Petri dish with a glass to prevent evaporation. When this was done, the cells disappeared after 2–3 min, the wavefronts became smooth and the reproduction of spiral waves stopped. In such experiments the development of chaos could be interrupted at any stage. For example, if this process did not go too far, only a few rotating spiral waves were observed. On removing the covering glass, the cells continued to appear, thus triggering the reproduction of spiral waves. The longer the reaction ran, the greater were the number of spiral waves and the smaller the scale of the wave pattern. At the later stages the picture resembled a small-scale turbulence, the characteristic size being of the order of a spiral wave core.

Our data show that in all the cases studied chaos was preceded by the appearance of convection cells. This means that this phenomenon can be adequately described by the theoretical scheme of the development of autowave chaos in a non-homogeneous medium^{3,4}, and the mechanism of chemical turbulence can thus be explained.

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Long-range attractive forces between two mica surfaces in an aqueous polymer solution

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High polymers are widely used as flocculants in aqueous colloidal dispersions^{1,2}. All direct investigations to date of the forces between surfaces bearing adsorbed polymers in good solvent media, however, have indicated a monotonically increasing repulsion, rather than attraction, as the surfaces approached³⁻⁸. We have now measured the interactions between two smooth mica surfaces immersed in an aqueous solution of polyethylene oxide (a good solvent system) in the range 0–300 nm apart, and find that at low adsorbance of the polymer on the mica there is a reversible, time-independent, long-range ($\sim 2.5 R_g$, the unperturbed radius of gyration of the polymer) attraction as the surfaces approach. On permitting equilibrium adsorption of the polymer to take place, the attraction disappears, to be replaced by monotonically increasing, long-range repulsion.

The experimental technique and apparatus, as described previously^{9,10}, permit the accurate measurement of forces $F(D)$ between two smooth curved mica surfaces (radius of curvature $R \approx 1$ cm) immersed in a liquid medium a closest distance D apart, in a convenient range $D = 0$ –500 nm. The procedure in our experiments was as follows: the interactions $F(D)$ between bare mica surfaces in 0.1 M KNO_3 were first determined, and the surfaces then separated to $D = 20 \mu\text{m}$. Polyethylene oxide (supplied by Toyo Soda, Japan; molecular weight 1.2×10^6 ; $M_w/M_n = 1.12$; $R_g = 35$ nm) was added to the system to a concentration of $10 \pm 1 \mu\text{g ml}^{-1}$, and the surfaces left to incubate in the solution to allow adsorption of the polymer to take place. At no time during the incubation period did the separation D between the surfaces exceed $\sim 20 \mu\text{m}$; as a result polymer molecules from the bulk solution had to diffuse a considerable lateral distance (~ 1 mm) through the narrow intersurface gap (20–100 μm wide) before reaching the region of closest approach between the mica sheets ($D = 20 \mu\text{m}$) and adsorbing onto the surfaces. Because of this, the rate of adsorption of polymer onto the mica in the region of interest, where $F(D)$ is measured, was severely reduced (relative to the corresponding rate of adsorption from bulk solution onto a free surface)¹¹ and several hours were required for the limiting adsorption of polymer to be attained, beyond which no further changes in the force profile were observed (see also Fig. 1). Hence, by measuring $F(D)$ at various times following the introduction of polymer, it was possible to monitor the surface-surface interactions as progressively more polymer adsorbed.

Figure 1 shows the change in $F(D)$ with time of incubation in the polymer solution. The force-distance profile between the mica surfaces before the addition of polymer is shown in Fig. 1a: close in ($D \leq 10$ nm), the interaction is strongly repulsive and characteristic of electrostatic double-layer overlap, while at $10 \text{ nm} \leq D \leq 15$ nm a weak, short-range attractive regime ('secondary minimum') is observed, in accord with earlier reports^{8,9}. Following addition of polymer and incubation for 1 h (at $D = 20 \mu\text{m}$), the secondary minimum disappears and strong repulsion is observed at $D \leq 20$ nm (Fig. 1b). After incubation for 2–3 h (at $D = 20 \mu\text{m}$), a clear attraction ($F(D) < 0$) between the surfaces is observed (Fig. 1c), commencing at $D = 90 \pm 10$ nm, with an attractive maximum at $D \approx 45$ nm; as the surfaces are brought closer together, the attraction decreases, and changes to an ultimate strong repulsion for $D \leq 20$ nm.

Once the surfaces are brought closer together to commence an $F(D)$ measurement (to $D \leq 300$ nm, after a given incubation

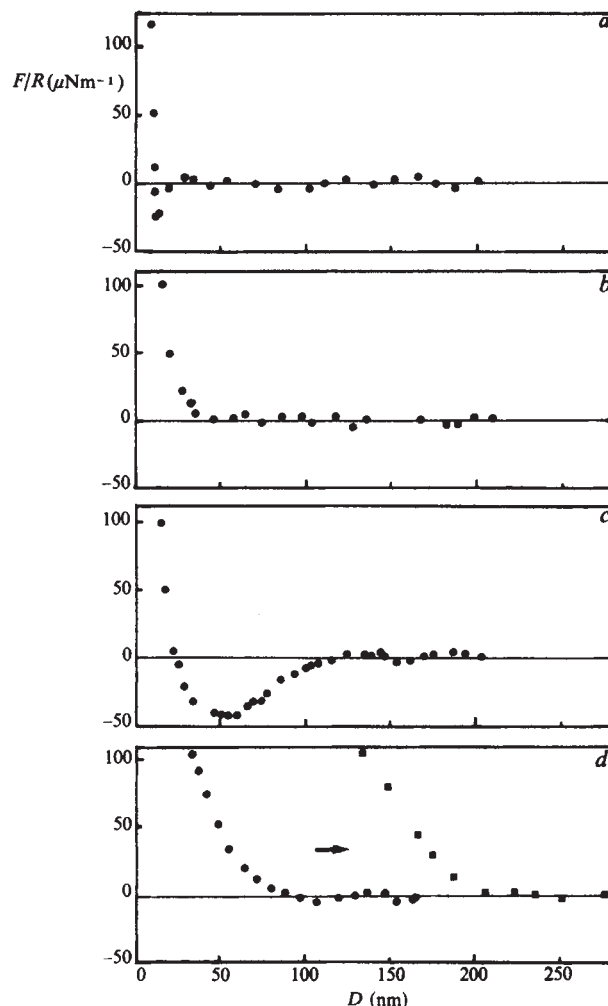


Fig. 1 Force ($F(D)$)–distance (D) profiles between two curved mica surfaces immersed in aqueous 0.1 M KNO_3 at $23 \pm 2^\circ\text{C}$, a closest distance D apart. The force scale is normalized as $F(D)/R$, where $R (\approx 1 \text{ cm})$ is the mean radius of curvature of the mica sheets, to give the surface energy per unit area between flat parallel plates obeying the same force law, in the Derjaguin approximation⁹. *a*, Before addition of polymer. *b*, After addition of polyethylene oxide and incubation of the surfaces at $D = 20 \mu\text{m}$ for 1 h. *c*, After incubation for 3 h in the polymer solution at $D = 20 \mu\text{m}$. *d*, After incubation for 8 h at $D = 20 \mu\text{m}$ (●) and after 32–48 h at $D = 20 \mu\text{m}$ (■).

period at $D = 20 \mu\text{m}$), the force–distance profile does not change appreciably with time until D is again increased to the incubation separation of $20 \mu\text{m}$. The attraction following 2 h of incubation persists up to 4–5 h incubation time (at $D = 20 \mu\text{m}$). After 6–8 h, however, the attraction disappears (Fig. 1d), and leaving the surfaces to incubate for longer times results in a monotonically increasing repulsion commencing at progressively larger D values, up to a limiting value $D \approx 180$ nm after overnight incubation (Fig. 1d). This limiting value of D for onset of repulsion does not increase on further incubation (up to 2 days).

Figure 2 shows the force–distance profiles from several compression–decompression cycles, following incubation times of 2–4 h (at a surface separation of $20 \mu\text{m}$); within error, the profiles are the same whether the surfaces are approaching (compression) or are being separated (decompression).

Our results show directly for the first time the existence of attractive long-range forces between two solid surfaces in good polymer solutions. This attraction depends on the extent of polymer adsorbance onto the surfaces: it is most marked at low adsorbance values, and disappears, changing to a long-range repulsion, as full (or limiting) adsorption of polymer is attained. This repulsion is probably due to osmotic interactions between the opposing polymer layers, as they come into overlap in the

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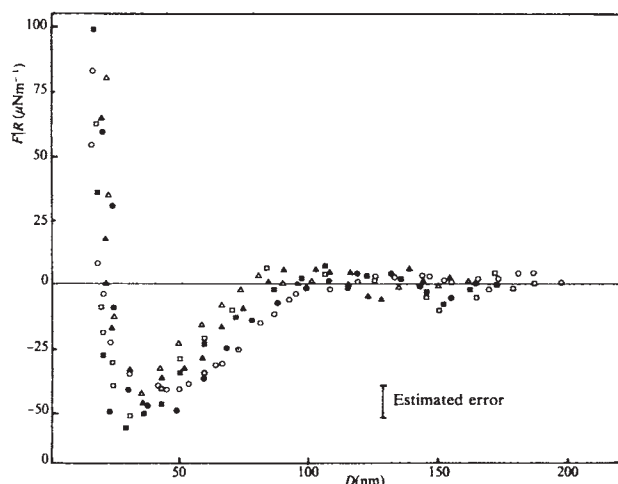


Fig. 2 Force-distance profiles (force scale normalized as in Fig. 1) between curved mica surfaces after incubation for 2–4 h at $D = 20 \mu\text{m}$ in $10 \mu\text{g ml}^{-1}$ polyethylene oxide solution in aqueous 0.1 M KNO_3 at $23 \pm 2^\circ\text{C}$. □, Compression of surfaces (surfaces approaching) after incubation for 2 h; ■, subsequent decompression (surfaces moving apart) after incubation for 2 h. ○, Compression after incubation for 3 h; ●, subsequent decompression; △, compression after incubation for 4 h (for a different experiment on a different pair of mica sheets); ▲, subsequent decompression.

good solvent conditions of the experiment⁸. The distance for onset of repulsion—once full adsorbance of polymer has been attained—is some $5\text{--}6 R_g$, a value consistent with earlier reports on the thickness of polyethylene oxide layers adsorbed onto mica in similar conditions⁸.

These observations have clear implications for the flocculation of colloids by added nonionic polymer: on initial adsorption of polymer onto the colloidal particles a strong attraction arises, as in Fig. 1c and Fig. 2; particles undergo brownian collisions and adhere to each other, leading to the formation of large aggregates, or flocs. This aggregation prevents further adsorption of polymer onto the particles, so that the attractive force persists, as in our experiments when the surfaces are brought close together following 2–4 h of incubation. (The attractive surface energy per unit area at the attractive maximum in our measured $F(D)$ profiles, $\sim 50 \mu\text{J m}^{-2}$, corresponds to an overall attractive energy of some 100 kT for two colloidal particles of $1 \mu\text{m}$ diameter, obeying the same force law, when 50 nm apart at room temperature. Once adhered, such particles would not readily separate under their thermal energy.)

Finally, we note that the origin of the attractive interactions observed following partial adsorption is probably due to bridging of the intersurface gap by polymer molecules adsorbed simultaneously on both mica surfaces. This effect is more significant at low (as opposed to full) surface coverage by the polymer for two reasons: (1) at low adsorption the concentration of polymer segments in the gap is also low, so that the repulsive osmotic interactions are weak relative to the attractive bridging forces and (2) local equilibrium at low surface coverage may be attained more rapidly, so that bridge formation—with consequent attraction—is favoured, over the measurement times in our experiments, relative to the full adsorption case.

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Rapid evolution of a Gulf Stream warm-core ring

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Gulf Stream warm-core rings form in the Slope Water between the North American continental shelf and the Gulf Stream by the separation of a north-extending meander¹. The initial physical, chemical and biological properties of the core of these $100\text{--}200\text{-km}$ eddies are often similar to those of its parent water mass, the Sargasso Sea. A clockwise rotating remnant of the Gulf Stream circulates around the core with surface current speeds of $50\text{--}200 \text{ cm s}^{-1}$. Although warm-core rings can slowly change over periods of months through interactions with the surrounding Slope Water, Gulf Stream meanders, continental slope, other rings, and the atmosphere, we have now discovered that major alterations to ring structure can occur during very short periods (2–5 days) when an interaction with the Gulf Stream is particularly intense. Such short-period interactions between a ring and the Gulf Stream are a major factor governing a ring's evolution.

The rapid transformation of a warm-core ring's structure was observed in some detail during the first cruise of a multi-disciplinary programme to examine the evolution of warm-core rings². The study began with satellite reconnaissance and the visit of the research vessels *Endeavor*, *Atlantis II* and *Albatross IV* to ring 81-D (the fourth warm-core ring to form in 1981) in September–October 1981. 81-D became detached from the Gulf Stream east of the New England Seamounts in July 1981. By early September it had moved to 40°N , 64°W and was elliptical, with major and minor diameters of 190 and 144 km . An eastward-propagating Gulf Stream meander interacted with warm-core ring 81-D between 16 and 24 September 1981, causing the latter's rapid transformation; the ring's radius decreased and a significant portion of Sargasso Sea water was lost from the ring's core to depths of nearly 1 km . Physical and biological properties of the surface water of the core were altered by exchanges with surrounding surface water.

Two surveys of the ring were made approximately 10 days apart (Fig. 1), the first by the *Endeavor* on 14–16 September, the second on 24–27 September by *Endeavor*, *Atlantis II* and *Albatross IV*. In the 8 days between the two surveys, a Gulf Stream meander (Fig. 1, upper right) had strongly interacted with the ring, resulting in a dramatic reduction of its horizontal extent and alteration of its vertical structure. During the first survey, satellite and shipboard measurements of the ring's surface-temperature field were in very good agreement. However, despite a large number of shipboard surface-temperature measurements during the second survey, they were insufficient to describe the ring structure as synoptically as the satellite imagery. This suggests that satellite observations of ocean colour might also show an image of the ring not evident from the shipboard survey of plant pigments (Fig. 1). This was not the

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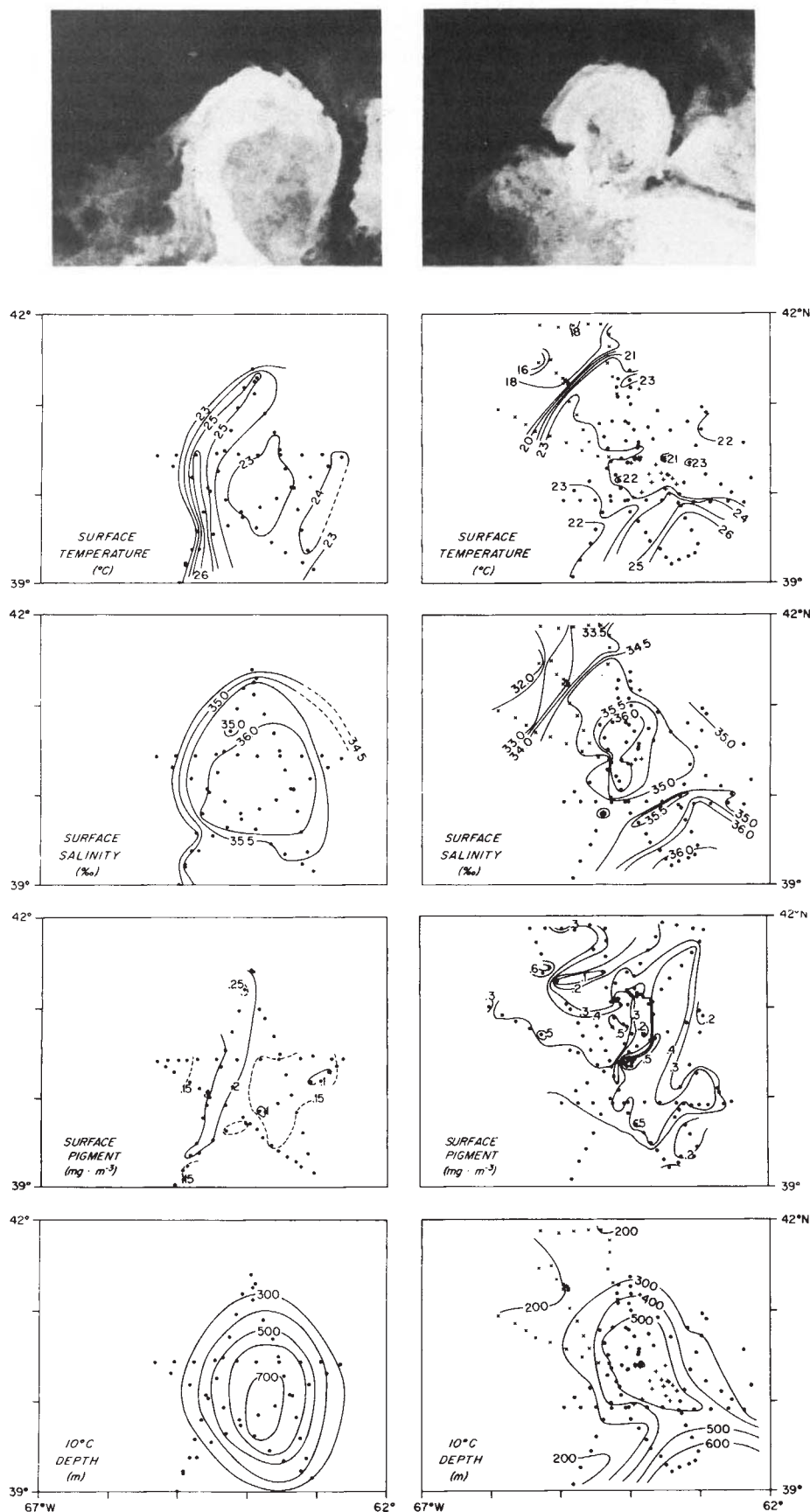


Fig. 1 Plan view of warm-core ring 81-D for days 257–259 (14–16 September) (left) and days 267–270 (24–27 September) (right). From top to bottom, satellite thermal imagery (AVHRR), *in situ* surface temperature ($^{\circ}\text{C}$), surface salinity (p.p.t.), mg pigment per m^3 , and depth (m) of the 10°C isotherm. 81-D is seen in composite satellite-derived sea-surface temperature maps obtained from the NOAA-7 IR radiometer (upper panel). Ring 81-D was delimited for the period of the first survey by the warm streamer of Gulf Stream on the west and the cold shelf-water streamer east of the ring centre. The surface salinity of the ring core was higher than that of the surrounding Slope Water and surface plant pigments ranged from 0.08 to 0.25 mg pigment m^{-3} with high values on the western edge of the ring and isolated low values to the east. Total pigments were determined by the fluorescence technique (R. Smith *et al.*, unpublished) and are the sum of chlorophyll *a* and phaeopigments. During the second survey the ring/meander were partially attached and the maximum depth of 10°C in the ring was <600 m. Surface salinities in the ring core were reduced in the second survey, while the range in surface pigments was greater (0.09 – 0.7 mg pigment m^{-3}) and the values generally higher. A region of minimum pigment (<0.1) was seen in both surveys at the edge of the ring where surface currents could have carried it completely around the ring in slightly less than 4 days.

case for 81-D at this time, however, as no clear ring signature was evident in the ocean colour imagery.

Vertical sections of temperature through 81-D (Fig. 2) show that major changes occurred between days 258 and 303 (15 September–30 October). The core of the ring initially contained a large amount of water with temperature near 18°C (layer

17 – 19°C ; Fig. 2a). This indicates an origin in the Sargasso Sea, where such water is usually found³ extending as a homogeneous mass from near the surface to depths of 500 m. A later *Endeavor* section through the ring centre (Fig. 2b) showed that the thickness of the layer of 18°C water had been reduced by 90 m as a result of the interaction with the Gulf Stream. This reduction

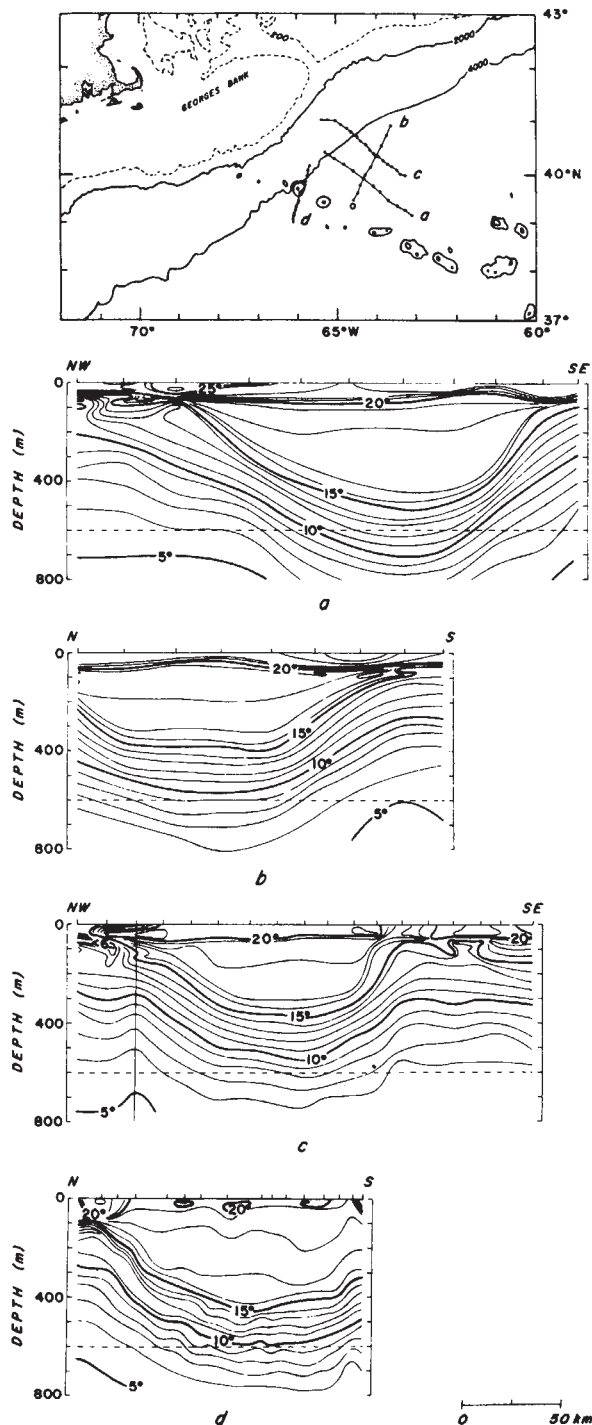


Fig. 2 Temperature sections through the centre of warm-core ring 81-D from: *a*, *Endeavor*, day 258 (15 September); *b*, *Endeavor*, day 271 (28 September); *c*, *Albatross IV*, day 277 (4 October); *d*, *Dawson*, day 303 (30 October). On one off-centre section from the first *Endeavor* survey (*a*) the depth of the 10 °C isotherm, which marks the main thermocline, changed from 200 m outside the ring to over 700 m inside.

was due to the redistribution of mass after a significant portion of the ring had been removed. Subsequent transects Fig. 2*c, d*) showed little change in the deeper structure of the ring despite its having moved westward across the New England Seamounts. On the edge of 81-D (above the regions of strongly sloping isotherms) near-surface currents of nearly 200 cm s⁻¹ flowed clockwise around the ring core⁴.

A time series constructed from selected water samples, expendable bathythermographs (XBTs), and conductivity, temperature, depth (CTD) stations near the ring centre shows some of the changes that occurred when 81-D and the Gulf Stream

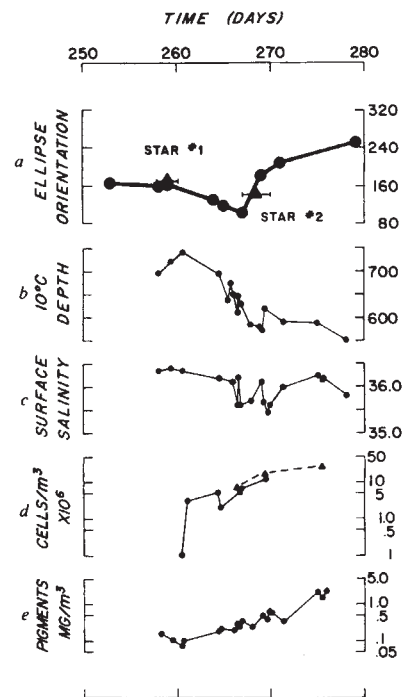


Fig. 3 Changes in warm-core ring 81-D of: *a*, ellipse orientation (deg true); *b*, depth of 10 °C isotherm (m); *c*, surface salinity (p.p.t.); *d*, coccolithophore standing crop at 10 m (number of cells); *Endeavor* (●) and *Atlantis II* (▲); *e*, total plant pigments (mg m⁻³). Note the logarithmic scale in the lower two panels. On day 266 (23 September) surface salinity near the ring centre rapidly decreased from 36.4 to 35.6 p.p.t. primarily due to a flooding of the ring centre by fresher water. Thereafter, variability was produced by local patchiness of low and high salinity water and wind-induced mixing events. Low plant pigment values were found initially in the centre of the ring, but they gradually increased during the cruise by more than an order of magnitude, with final values of 2.0 mg m⁻³ on day 275 (2 October) (*e*). In comparison, a Sargasso Sea station on day 272 (29 September) had a surface-water phytoplankton pigment value of 0.14 mg m⁻³ (0.10 chlorophyll *a*, 0.04 phaeopigment). The phaeopigment/chlorophyll ratio remained roughly constant in the ring centre. Coccolithophore standing crop in the ring centre increased over 100 times during the period of observation, from 0.1 to 27 × 10⁶ cells m⁻³ (*d*). Sampling of the Gulf Stream, Sargasso Sea and Slope Water showed no parallel increase. The initial (day 260, 17 September) coccolithophore samples from shallower than 10 m in the ring centre were dominated by *Emiliania huxleyi*, and this species continued to dominate the flora throughout the sampling period. Six ring-centre samples from 50 m contained a different 'deep water' coccolithophore flora¹⁵⁻¹⁷ dominated by *Florisphaera profunda*, *Hayaster perplexus* and *Thorosphaera flabellata*. Thus, the observed increase in the coccolithophore standing crop at 10 m in the ring centre after day 261 (18 September) must be accounted for by *in situ* growth.

interacted (Fig. 3). Satellite imagery has been used to estimate the position of the ring centre and to fit an ellipse to the ring by least-squares⁵; the orientation of the major axis is plotted together with depth of the 10 °C isotherm, surface salinity, coccolithophore standing crop at 10 m and surface plant pigments. During the 8-day period between the two maps of Fig. 1, the ring axis rotated from nearly north-south to north-west-south-east, the thermocline depth decreased by 120–150 m (with the most rapid decrease occurring during the 4 days centred on day 266, 23 September), and surface salinity was temporarily reduced from 36.4 to 35.6 parts per thousand (p.p.t.). After day 267 (24 September) the ellipse axis changed direction of rotation.

The rapid change in the ring during its interaction with the Gulf Stream resulted in a 60% decrease in the energy associated with the thermocline depression in the ring centre, but an increase in the intensity of the swirling flow around the ring.

The available potential energy (APE) is associated with the bowl-shaped depression of the thermocline relative to the surrounding Slope Water and is defined as the energy that would be released by an adiabatic relaxation of the thermocline to a level surface^{6,7}. Before interaction with the Gulf Stream, APE is estimated from an XBT section made on day 259 (16 September) to be 1.3×10^{16} J. Calculation from a cross-section made on day 271 (28 September), immediately after the interaction, yields an estimate of 5.2×10^{15} J. The loss of APE during the ring's contact with the Gulf Stream and its subsequent readjustment occurred at a rate of ~ 7.7 GW, which is at least an order of magnitude larger than that observed in warm- and cold-core rings outside the influence of the Gulf Stream⁸. It also exceeds the barotropic energy flux observed on the continental slope in connection with the formation of a warm-core ring⁹. The available potential energy lost in the September 1981 interaction probably went into the Gulf Stream.

As the ring lost energy and shrank, the magnitude of the relative vorticity, $|\zeta|$, a measure of the strength of the ring vortex, increased. ζ is equal to the sum of the radial shear in the ring's currents, $\partial v / \partial r$, and the angular velocity of the flow, v/r . This quantity is negative ($\zeta < 0$) for an anticyclonic, warm-core ring. Directly observed near-surface currents⁴ suggest a 10% increase in $|\zeta|$ for the surface layer of the ring during the Gulf Stream interaction. This increase was accompanied by a decrease in the thickness of the layer of 18 °C water in the core of the ring, Δh . The decrease agrees (to within 20%) with the change estimated from the increase in $|\zeta|$ and the conservation of potential vorticity $(f + \zeta) / \Delta h$ (where f is the Coriolis parameter)¹⁰ in the fluid remaining in the ring.

Coincident with the maximum change in ring structure near day 266 (23 September, Fig. 3) was a change in certain species of midwater organisms occurring in the ring core. A highly specialized fish fauna, living by day at depths of 500–800 m and by night in the upper few centimetres, was caught in a neuston net towed from the *Atlantis II*. Fifteen collections were made in the ring centre within a few hours of local midnight on four successive nights. Moderate catch rates were observed on days 264 and 265 (averages of 26.5 and 33.6 fish per h) but they were significantly lower on days 266 and 267 (averages of 4.8 and 1.0 fish per h). The catch on the first two nights consisted mostly of two myctophid fishes, *Goniichthys cocco* and *Centrobranchus nigroocellatus*¹¹. These species almost wholly disappeared from the catch on the third and fourth nights, whereas the astronethid fish *Astronesthes niger* became more abundant. These changes were probably due to ring centre flooding some time before 0545 GMT, day 266 (23 September) during a period of darkness, when the neuston fauna was susceptible to removal. This abrupt shift coincides with the first appearance in the centre of the ring of low salinity water having a large Slope Water component (Fig. 3c).

The changes in subsurface structure of the ring were evident in the catches of *Cyclothone* spp., non-vertically-migrating midwater fishes that live at depths from ~ 400 to 2,000 m^{12,13}. Two species, shallower-living *Cyclothone braueri* and deeper-living *Cyclothone microdon*, have different vertical distributions in the Slope Water and northern Sargasso Sea. They were caught in three plankton tows (0–1,000 m) in the ring centre on days 264, 267 and 274 (21 and 24 September and 1 October). The first collection contained some *C. braueri* at 700–800 m. The last contained none from deeper than 500–600 m. The first collection contained no *C. microdon* from shallower than 600–700 m, but the last contained some in the 500–600 m stratum. The second collection was intermediate in these respects. Similarly, the vertical distribution patterns of copepods living deeper than 500 m (for example, *Calanus finmarchicus*, *Calanus hyperboreus*, *Metridia lucens*, *Metridia venusta* and *Metridia brevicauda*) shoaled ~ 100 m between days 264 and 274. These changes in vertical distribution coincide with and are explainable by the rapid shoaling of the 10 °C isotherm depth and loss of 18 °C water in the ring centre that took place between days 264 and 268 (21 and 25 September) when physical and chemical

characteristics of the ring centre between 500 and 700 m became less like the Sargasso Sea and more like the Slope Water.

While deep- and shallow-living components of the ring-centre biota give evidence of substantial change coincident with the ring/Gulf Stream interaction, this was not true for members of zooplanktonic groups living at intermediate depths. For example, the abundance and composition of those euphausiids (*Nematoscelis microps*, *Nematoscelis tenella*, *Stylocheiron abbreviatum*, *Stylocheiron affine*, *Stylocheiron suhmii* and *Stylocheiron elongatum*) living principally between 75 and 500 m and not performing a diel vertical migration into surface waters at night, changed little in the three plankton tows which bracketed the period of maximum change. These species were rare or absent in plankton samples from the adjacent Slope Water. Aside from the significant loss of mass, the physical properties of this part of the ring-water column showed little change.

The rapid evolution of warm-core ring structure due to intense ring/Gulf Stream interaction was also observed during the time-series study of ring 82-B from April to August 1982. From satellite observations of the surface properties of warm-core rings undergoing Gulf Stream interactions coupled with *in situ* observations of the effects of these interactions on ring structure, we conclude that the alteration of warm-core rings proceeds mainly by episodic interactions with the Gulf Stream. The lower probability of interactions in the case of Gulf Stream cold-core rings¹⁴ is probably responsible for the substantially longer lifespan and the more evenly paced evolution of this kind of ring.

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Sterenes in suspended particulate matter in the eastern tropical North Pacific

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Particulate matter in the oceans is operationally partitioned into two pools. Large ($\geq 32 \mu\text{m}$) particles, such as zooplankton faecal pellets and marine snow, sink rapidly and dominate the vertical flux of organic matter in the oceans^{1–4}. These relatively rare particles, usually collected in sediment traps, sink at rates of tens to hundreds of metres per day^{5–8} leading to a significant flux of labile particulate organic matter from sites of production in the euphotic and mesopelagic zones to the deep ocean^{9–14}. Finer ($\leq 2 \mu\text{m}$) suspended material, on the other hand, dominates the standing stock of particulate matter¹. Sinking rates of only a few metres per day for small particles result in long

residence times in the water column during which major transformations of the suspended organic matter may occur. Source and transformation processes involving particulate organic matter in seawater and Recent sediments may be traced by studying various classes of specific organic marker compounds, including the steroids^{9,11,15-18}. We report here the apparent production of sterenes (steroidal alkenes) on suspended particulate matter within the oxygen minimum zone in the equatorial Pacific Ocean off central Mexico; this provides further evidence of the importance of water column processes on early stages of the transformation of biogenic sterols to the steranes present in mature sediments.

Suspended particulate matter samples were collected during the VERTEX II and III cruises in October 1981 and November 1982, respectively, off the west coast of Mexico (15–19° N, 107–109° W). The most notable feature of this area is its oxygen minimum zone extending 100–800 m, in which the O₂ concentration drops to <1 µmol kg⁻¹ at 120–140 m (Fig. 1)^{19,20}. A primary fluorescence maximum near 60 m correlates with chlorophyll *a* concentrations indicative of the phytoplankton biomass maximum, while a secondary fluorescence peak at 130–140 m in the O₂ minimum is related to a maximum in heterotrophic bacterial activity (ref. 20 and D. M. Karl, personal communication). Denitrification has been observed between about 100 and 250 m (ref. 21 and C. Lee, personal communication). Mean primary productivities of about 860 and 470 mg C m⁻² day⁻¹ (integrated over the 100-m mixed layer) were measured in 1981 and 1982, respectively (G. A. Knauer, personal communication).

The samples were collected at several depths (Fig. 1) at night using Woods Hole In Situ Pumps (WHISPs), which are hydrographic-wire mounted, stream-powered, large volume filtering systems (F. R. Hess, in preparation). Four hundred to 4,000 l of seawater were pumped through ashed glass fibre filters (293 mm, type A/E; nominal pore size 0.3 µm) during 8–12 h deployments. Pumping large volumes increases the chance of collecting a few large particles, and a few zooplankton and faecal pellets from the red crab *Pleuroncodes planipes* were seen on some filters. Analyses of other samples of these materials showed sterenes to be absent. Following recovery, the filters were frozen

and returned to the shore-based laboratory. The filters were Soxhlet extracted with toluene/methanol (1:1) and the lipids fractionated according to functionality by adsorption chromatography (Merck silica gel 60 5% deactivated with water). The hydrocarbons discussed here were eluted with hexane; other lipids (wax esters, triacylglycerols, fatty alcohols, and steroidal alcohols, ethers, and ketones) were sequentially eluted⁹, and these results will be described elsewhere. It was not necessary to separate further saturated and unsaturated hydrocarbons. Gas chromatography was carried out using a Carlo Erba 4160 gas chromatograph with on-column injector and glass capillary columns deactivated by persilylation and coated with cross-linked SE-52 (ref. 22). Gas chromatography/mass spectrometry analyses were performed with a system combining a Carlo Erba 4160 gas chromatograph, a Finnigan 4500 mass spectrometer and an Incos 2300 data system. Sediment trap samples were also collected, but detailed results are beyond the scope of this paper.

Sterenes in the WHISP particulate samples had a strong concentration maximum at 140 m, the depth of the minimum O₂ concentration (Fig. 1). Total lipids and sterols (sterol plus stanol), on the other hand, had concentration peaks at 60 m where phytoplankton and zooplankton biomass were greatest. Thus sterenes were present in higher relative abundances in the O₂ minimum, in which a sterene:lipid ratio of 53.7×10^{-4} was found at 140 m, compared, for example, with 3.4×10^{-4} and 7.2×10^{-4} at 60 m and 950 m, respectively. The abundance of sterols was fairly constant with increasing depth (sterol:lipid = 3.4×10^{-2} , 3.3×10^{-2} and 2.0×10^{-2} at 60 m, 140 m, and 950 m). Sterenes were a major portion of the total hydrocarbons in the O₂ minimum, comprising 88% of the hydrocarbons at 140 m compared with 8% and 30% at 60 m and 950 m, respectively.

The distribution of individual sterenes was complex, with up to 25 compounds present representing C₂₇, C₂₈ and C₂₉ monoenes, dienes, trienes and traces of tetraenes (Fig. 2, Table 1). Structural assignments (Table 1) were made from gas chromatographic retention times of several authentic standards, the Δ^4 - and Δ^5 -cholestenes and $\Delta^{4,22}$ - and $\Delta^{5,22}$ -steradienes isolated from the immature Monterey shale²³, and by mass spectral interpretations^{16,23-31}. Cholest-2-ene and cholesta-3,5-

Table 1 Sterenes assigned in WHISP particulate matter samples

Designation (Fig. 2)	Assignment	Concentration 140 m (µg l ⁻¹ × 10 ⁵)
a	Cholesta-N*,22-diene	17
b	Cholesta-N,22-diene	34
c	Cholestatriene	6
d	Cholesta-N,24(28)-diene	18
e	Cholest-2-ene	84
f	Cholesta-N,N,24-triene	130
g	Cholesta-N,22-diene/minor cholestatetraene,24-methylcholestadiene	52
h	Cholesta-3,5-diene	260
i	Cholestatriene	12
j	Cholesta-N,3,5-triene	100
k	Cholesta-N,N,24-triene	74
l	24-Methylcholesta-N-24(28)-diene/24-methyl-cholesta-N,N,24(28)-triene (1:1)	81
m	24-Methylcholest-2-ene/minor 24-ethylcholesta-N,24(28)-diene	21
n	24-Methylcholesta-N,24(28)-diene	48
o	24-Methylcholesta-N,N,24(28)-triene	80
p	24-Methylcholesta-3,5-diene	10
q	24-Methylcholesta-N,N,24(28)-triene	52
r	24-Ethylcholestene	7
s	24-Methylcholesta-N,N-diene/minor cholestatetraene	5
t	24-Ethylcholest-2-ene	7
u	Cholestatriene	9
v	24-Ethylcholesta-N,24(28)-diene	35
w	24-Ethylcholesta-3,5-diene	2
x	24-Ethylcholesta-N,N,24(28)-triene	1
y	24-Ethylcholesta-N,N,24(28)-triene	2
	Total	1,150
1	Hop-22(29)-ene	30

* N, 5,6 nuclear unsaturation at unknown position, but probably not Δ^2 , Δ^4 or Δ^5 .

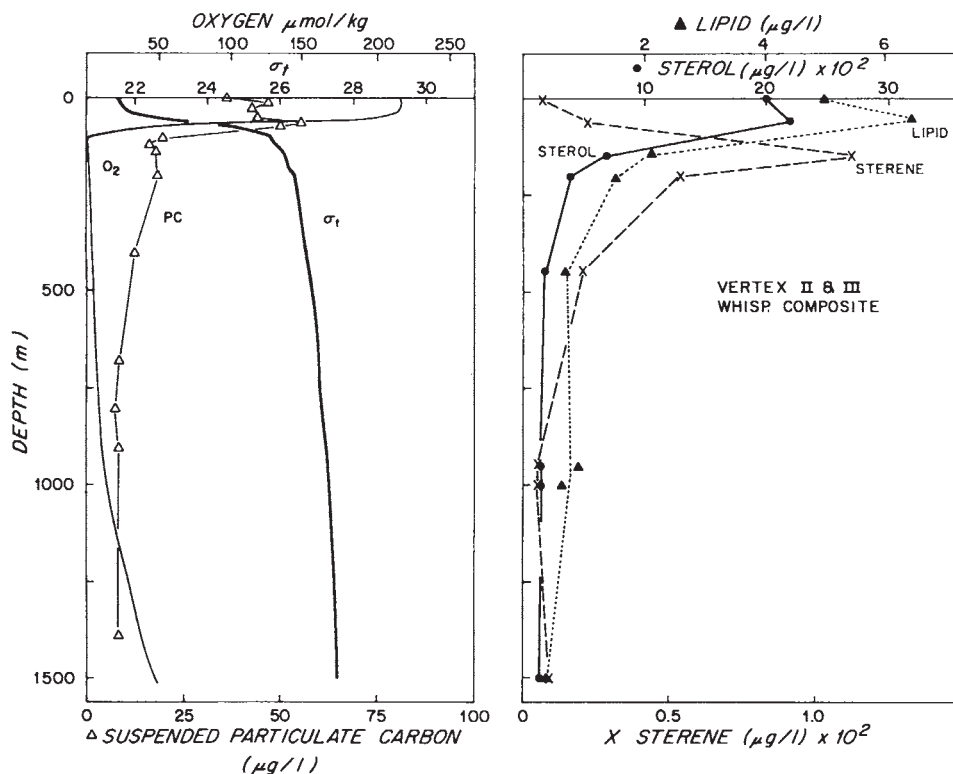


Fig. 1 Vertical distributions of density (σ_t), dissolved oxygen, and suspended particulate carbon (G. A. Knauer and J. H. Martin, personal communication) (left panel), and composite depth profiles for concentrations ($\mu\text{g l}^{-1}$) of total lipids (gravimetric), sterols (stenols and stanols) and sterenes collected by the WHISPs during VERTEX II and III (right panel). VERTEX II sample depths: 5 m, 200 m, 1,000 m; VERTEX III depths: 5 m, 60 m, 140 m, 450 m, 950 m, 1,500 m. The values for 5 m are means of values for the 2 yr, which agreed to better than 10%. Profiles are composites of data from 2 yr: 1981—5 m, 200 m, 1,000 m; 1982—5 m, 60 m, 140 m, 450 m, 950 m, 1,500 m. The profiles were essentially the same, considering differences in sample depths, and were relatively independent of differences in primary productivity. The discussion focuses on the 1982 profile.

diene co-eluted with standards on three capillary columns (SE-52, OV-1701 and Pluronic 64). The WHISP samples did not contain C_{30} -sterenes, Δ^4 - or Δ^5 -sterenes, diasterenes, A-ring monoaromatic steroids or steranes.

At all depths, C_{27} -sterenes dominated. C_{27} -sterenes accounted for 49–69% of total sterenes compared with 26–40% for C_{28} - and 3–25% for C_{29} -compounds. This trend parallels the sterol distributions in the same samples. Steradienes and steratrienes were generally more abundant than the corresponding monosterenes. Furthermore, relative abundances of monoenes, dienes and trienes changed as water depth increased, with the major shift occurring at the top of the O_2 minimum zone. For example, the ratio of $\text{C}_{27} + \text{C}_{28} + \text{C}_{29}$ -monoenes: dienes: trienes was 1.0:2.8:1.8 at 60 m, 1.0:4.3:4.7 at 140 m and 1.0:5.0:6.8 at 950 m. The relative lack of monoenes, of which Δ^2 -cholestene was the major constituent, contrasts with several Recent sediments in which monoenes often dominate the overall sterene assemblage^{16–18,31}. The surface sediment 'floc' from the VERTEX site contained a sterene distribution dominated by cholest-2-ene and cholesta-3,5-diene and was quite different from the 140-m WHISP sample illustrated in Fig. 2.

It has been previously postulated^{9,15–18,31} that sterenes are early diagenetic transformation products of sterols of biogenic origin, with the reactions occurring both in the water column and surface sediments. Known biogenic sources of sterenes in marine organisms are limited to a single report of cholesta-3,5-diene in the isopod *Ligia oceanica*³², and we found no sterenes in planktonic organisms or their faecal matter collected on the VERTEX cruises. The formation of monosterenes is thought to involve dehydration of stanols, which are either biogenic compounds or reduction products of precursor Δ^5 -stenols. Steradienes are direct dehydration products of stenols¹⁷. Thus in several Recent sediments, a correlation has been observed between individual monosterene/stanol and steradiene/stanol pairs, as well as totals for the classes¹⁷. In the VERTEX WHISP samples, similar relationships between the total classes also hold. Monosterenes and stanols are relatively minor components compared with steradienes and stenols. Furthermore, the relative abundance of monosterenes decreases in the water column below the euphotic zone (18% of total sterenes at 5 m compared

with about 10% at 140 m and deeper). Stanols are enriched in the O_2 minimum zone relative to stenols (for example, cholestanol:cholesterol = 0.04, 0.10 and 0.06 at 60 m, 140 m, and 950 m respectively), thus suggesting that reduction of stenols to stanols and then to monosterenes occurs at these depths. Alternatively, stenols may be selectively degraded, and/or stanols of biogenic origin enriched. In the case of steratrienes, the apparent absence of ring-diunsaturated stenols in the WHISP samples indicates that simple dehydration of stenols does not occur. Alternatively, as has been suggested for sediments¹⁶, hydroxylation of a Δ^5 -stenol or a steradiene and subsequent dehydration might produce the trienes. We have no data on steroid diols which would be intermediates in this pathway.

Many of the sterenes in the WHISP samples contained $\Delta^{24(28)}$ -unsaturation (Table 1), although the positions of ring unsaturation are usually unknown. This observation agrees with the abundance of $\Delta^{24(28)}$ -stenols (for example, 24-methyl- and 24-ethylcholesta-5,24(28)-dien-3 β -ols). On the other hand, relatively few Δ^{22} -sterenes were observed, although Δ^{22} -sterols were abundant in the samples. 4-Methyl-sterols of presumed microbial or dinoflagellate origin were present in the suspended particles at levels up to about 7% of the 4-desmethylsterols, but 4-methylsterenes were not detected, as is consistent with sediment analyses^{16,17}.

The abundance of sterenes on suspended particles in the O_2 minimum zone, where microbial activity is most intense, is strong evidence for a microbial transformation of steroidal precursors. Actual microbial production of sterenes has not been demonstrated, but microbial hydroxylations, dehydrations, and reductions of sterols are widely known^{33–36}. Since monosterenes are postulated to arise from stanols, microbially-mediated dehydration of the stanol, as well as microbial production of the stanol itself by reduction of a stenol may lead to the observed Δ^2 -monoenes, albeit at low levels. Further evidence of bacterial alteration of the organic matter in the suspended particles sampled is given by the presence of hop-22(29)-ene ('1' in Table 1 and Fig. 2) which is present in several bacteria^{37–39} and has been used as an indicator of bacterial diagenesis⁴⁰. While it is not possible to rule out purely chemical reactions in the O_2 minimum zone as the source of the observed sterenes it is

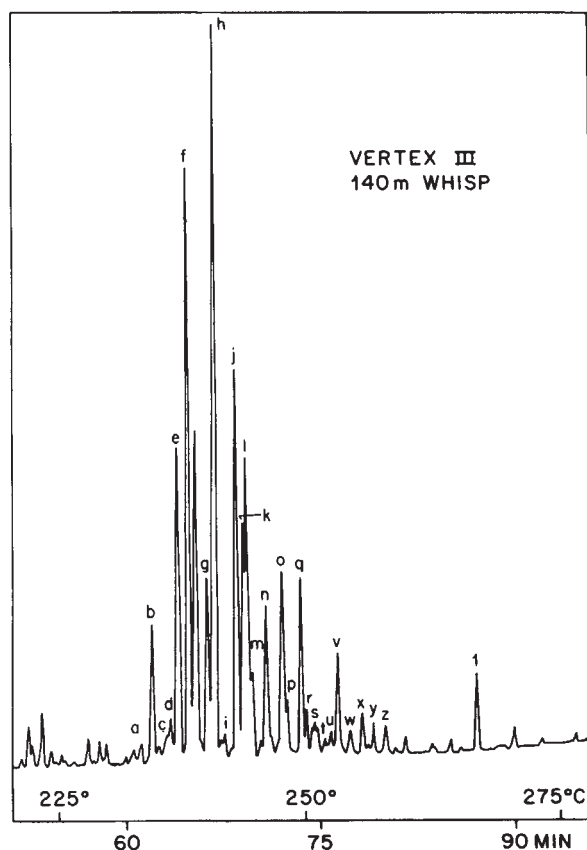


Fig. 2 Gas chromatograph of the total hydrocarbons in the VERTEX III 140 m WHISP sample. Conditions: SE-52, 30 m $\times$ 0.3 mm i.d., on-column injection, 1.5 $^{\circ}\text{C min}^{-1}$, 150–280 $^{\circ}\text{C}$, H_2 carrier 0.2 kg cm^{-2} , flame ionization detection. Peak designations refer to Table 1. The unlabelled peak between *f* and *g* is an unidentified non-steroidal hydrocarbon.

important to note that acid- and clay-catalysed dehydrations of cholesterol⁴¹ and cholestanol^{42,43} yielded predominately Δ^2 -, Δ^4 - and Δ^5 -cholestenes, none of which dominated the WHISP samples. Chemical autooxidations may be involved in the formation of a variety of diol intermediates¹⁶.

The strong concentration peak for sterenes in the O_2 minimum relative to deeper samples suggests that downward transport of sterene-rich small particles (WHISP samples) is not extensive. On the other hand, initial analyses of larger-sized material collected in sediment traps shows an enrichment in sterenes at depths in and below the O_2 minimum zone. For example, during the 1981 cruise, a sterene:lipid ratio of 1.5×10^{-4} in 50 m sediment trap material was found, while samples from 100 m, 470 m, 1,000 m, and 1,500 m had ratios over the range $12\text{--}42 \times 10^{-4}$. Sterol:lipid ratios in the same samples ranged from $22\text{--}77 \times 10^{-2}$, with no clear change across the O_2 minimum. Compound distributions for sterenes in the sediment trap samples were similar to those of WHISP particles. Thus aggregation of sterene-rich small slowly sinking particles in the O_2 minimum zone into larger, faster sinking particles (for example, faecal pellets and marine snow collected by sediment traps) may be one mechanism by which sterenes are rapidly transported vertically to the deep ocean and sediments. From the low levels of sterenes in WHISP samples below about 500 m, production of sterenes on the small particles as they sink is less extensive.

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Helping behaviour in brown hyenas

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The degree of relatedness between individuals is one of the primary factors influencing nonparental aid or 'helping behaviour'¹. However, in the field it is often difficult to determine precisely the familial relationships between helpers and recipients, and thus to assess the relative benefits of helping. Here we describe the results of a 7-yr study of brown hyenas in which most kinships were known, and report asymmetries in helping among clan members according to sex and relatedness. Natal males emigrate more often than females and provision cubs less frequently. Females provision young as distantly related as second cousins, while males provision half sibs, but not cousins. Such discrimination in nonparental aid between relatives has not been previously reported in large mammals other than primates².

Brown hyenas (*Hyaena brunnea*) were studied in the Central Kalahari, Botswana, from 1974 to 1981. Adults were ear tagged ($N=17$), radio collared ($N=9$) and monitored from aircraft and truck. Observations were made of six litters at one communal den (1,011 h). Since the primary clan was observed for 7 yr, familial relationships of most of its members were known.

Central Kalahari brown hyenas live in small clans, whose members forage solitarily and do not hunt communally³.

Table 1 Provisioning frequencies of clan members to six litters of cubs in 1,011 h

Individuals	Provisioning events	% Provisioning events	Robbing events	%
Mothers ($N = 6$) ($r = 0.5$)	43	21.3	0	0.0
Adult females (aunts, cousins) (13) ($r = 0.25$ to ≤ 0.03)	87	43.1	0	0.0
Subadult female cousins (3) ($r = \leq 0.03$)	49	24.2	0	0.0
Subadult males half sibs (2) ($r = 0.25$)	23	11.4	0	0.0
Subadult male cousins (4) ($r = \leq 0.03$)	0	0.0	14	100
Adult male immigrant (2) (r uncertain)	0	0.0	0	0.0
Total	202			
Nonparental aid	159	78.7		

The figures represent the provisioning events and frequency percentages of each class of clan member to six litters, including two litters of orphans. Another litter was later orphaned. Besides mothers, there were no females more closely related to cubs than aunts, first cousins once removed, and second cousins (grandchildren of full sibs, $r = 2$ (0.5))⁶. The relatedness of immigrant males to cubs is uncertain due to the populations of clan females by nomadic males.

However, clan members scavenge carrion together, defend a common territory and communally rear their young⁴.

The clan consisted of one to five related adult females, their offspring of various ages, and one dominant male. The females maintained a dominance hierarchy through such social interactions (374 observations) as escalated neckbiting combat³. Two of nine natal females left the clan following repeated neckbiting by dominant females.

Usually only one female gave birth to cubs each year, and there appeared to be competition over breeding opportunities. On one occasion when PA, the most dominant female, and DU her subordinate, had cubs at the same time, PA repeatedly neckbit and harassed DU. DU abandoned her litter and then suckled and provisioned PA's cubs. Similar competition was observed in red foxes⁵. However, unlike red foxes and some other social carnivores in which only the dominant female breeds (wild dogs^{6,7}, wolves⁸, mongooses⁹), even the most subordinate brown hyena female occasionally reared cubs at the communal den. The prolonged development of the dominants' cubs (18 to 24 months) provided opportunities for subordinates to reproduce before higher ranking females bred again. Regardless of their social rank, all females who were allowed to remain in the clan eventually reproduced.

The primary male mating system observed in 52 of 79 months, was for one immigrant male ($N = 2$) to defend the territory and to mate with females. However, each dominant male probably did not sire more than two successive litters because tenure of males was relatively short (27 and 26 months), development of cubs was prolonged, and only one female gave birth to cubs a year. Nomadic males without territories also courted clan females in 2 of 11 consortships and 1 clan female was observed copulating with a nomadic male. In 56 encounters the immigrant male always dominated natal males, of which six out of eight (75%) left the clan by the time they were 40 months old.

Females gave birth to one to four cubs (mean 2.0, six litters) in solitary dens. After 2.5–3.0 months, mothers carried cubs to the communal den where all young were reared by clan females^{4,10} and males¹¹.

Nonparental aid in brown hyenas included communal suckling, food provisioning, den maintenance, defence against predators, play¹⁰ and adoption of orphans. Nonparental food provisioning for all six litters constituted 159 of 202 (78.7%) of all feedings observed other than nursing (Table 1). This type of aid made up 50.0% ($N = 8$), 47.0% ($N = 17$) and 31.7% ($N = 22$) of aid given to litters 1, 2 and 4, in which cubs were not orphaned, and 60% ($N = 25$), 100% ($N = 23$) and 93.4% ($N = 107$) in orphaned litters 3, 5 and 6.

All females, regardless of social rank and degree of relatedness, including nulliparous and pregnant individuals, provisioned

cubs. Three lactating females, including two who had lost litters, suckled cubs other than their own offspring. Female helpers were no more closely related to the cubs than aunts, first cousins once removed, and second cousins ($r = 0.25$ to ≤ 0.03).

Nonparental adult and subadult females ($N = 16$) accounted for 136 of 159 (85.5%) of nonparental provisioning acts observed for six litters. Before emigrating, two of six natal males participated in provisioning, but in only 14.4% of the events. There was a significant difference between male and female helping ($\chi^2 = 13.14$; $P < 0.001$). Subadult females (24–40 months, $N = 2$) provisioned cubs 2.13 times as often as did subadult males ($N = 4$), ($\chi^2 = 39.06$; $P < 0.001$) (Table 1).

Eight of 10 cubs (three of five litters) reared to maturity were adopted orphans. One of six litters did not survive and one of the three adoptions occurred after the study period. Nonparental females ($N = 3$) provisioned ST's orphans in 82.1% (83 of 101) of observed provisioning events. Of the three natal males, only the half sib of the orphans provisioned them 17.8% (18 of 101) of observations. Female and male provisioning was significantly different ($\chi^2 = 41.8$; d.f. = 1; $P < 0.001$). Orphans of the other female (OL) were provisioned 23 times by three females, but never by males ($N = 2$) ($\chi^2 = 15.33$; d.f. = 1; $P < 0.001$). Thus, the observed orphans were helped more by females than by males.

Only males most closely related to infant cubs (known to be half sibs, $r = 0.25$) provisioned them. Males more distantly related than half sibs did not provision and on 14 occasions second cousins ($r = \leq 0.03$) removed and ate food items brought to the den by other individuals. Male half sib and male cousin provisioning differed significantly (Fisher exact test, $P = 0.027$). Four subadult males had opportunities to aid younger cousins in a total of seven litters, but did not provision them. However, two of these males provisioned their half sibs. Subadult males played with their cousins and helped maintain the den's chamber by digging out loose sand. We never saw immigrant males provision, play with cubs or maintain the den.

Females who received help when they were cubs later provisioned their helper's offspring, and adult females of similar ages provisioned one another's cubs. Subadult males did not always provision their helper's offspring, although they were as closely related to the cubs as were subadult females.

According to kin selection theory^{1,12}, the inclusive fitness of male and female helpers would be increased by aiding closely related cubs. Since most females remain in the clan and eventually breed, they acquire additional benefits from increasing clan size, and thus gain by aiding distant as well as close relatives. A larger clan would include more females who would later be available to provision the female helper's offspring and more individuals to defend the territorial resources. Because most males emigrate, they would not benefit from a larger clan and

thus would not gain as much as females by provisioning distant relatives.

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Prenatal development of individual retinogeniculate axons during the period of segregation

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When connections are first formed during the development of the vertebrate nervous system, inputs from different sources are frequently intermixed and the specific adult pattern then emerges as the different inputs segregate from each other^{1–11}. During the prenatal development of connections between retina and lateral geniculate nucleus (LGN) in the cat, the projections from the two eyes initially overlap with each other within the LGN. Over the next 3 weeks a reduction in the amount of overlap occurs so that by birth, a segregated pattern similar to the adult is present⁹. We report here that during the period of overlap, individual retinogeniculate axons are simple in shape and restricted in extent without any widespread branches. Further, the appearance of the segregated pattern of eye input is accompanied by the elaboration of extensive new axonal arbors within appropriate LGN territory accompanied by retraction of only a limited number of minor branches. This developmental strategy contrasts with that in other regions of the vertebrate central nervous system in which the orderly adult pattern of connections within a target is achieved by a relative reduction in the overall extent of the axon arbor^{5,12,13}.

To study the morphology of individual retinogeniculate axons during the prenatal process of segregation, we have developed an *in vitro* method for filling axons with horseradish peroxidase (HRP) in the fetal central nervous system (CNS). Animals of known gestational ages were delivered by caesarean section under anaesthesia⁹. The diencephalon including both lateral geniculate nuclei and the optic tracts was isolated, placed in a modified slice chamber and superfused with oxygenated Ringer's at 34–35 °C. Preparations maintained in this manner remain viable for up to 10 h as assessed by electrophysiological recordings from the LGN¹¹. Small deposits of HRP were made in the optic tract using glass micropipettes with HRP (Boehringer type I) coated tips. Following a 6-h postinjection survival period, the preparation was fixed⁹ and sectioned on the vibratome at 100 µm in the horizontal plane. (The major axis of the trajectory of retinogeniculate axons lies in the horizontal plane throughout prenatal development.) Sections were reacted for HRP histochemistry using diaminobenzidine with cobalt chloride intensification¹⁴ and individual labelled axons were

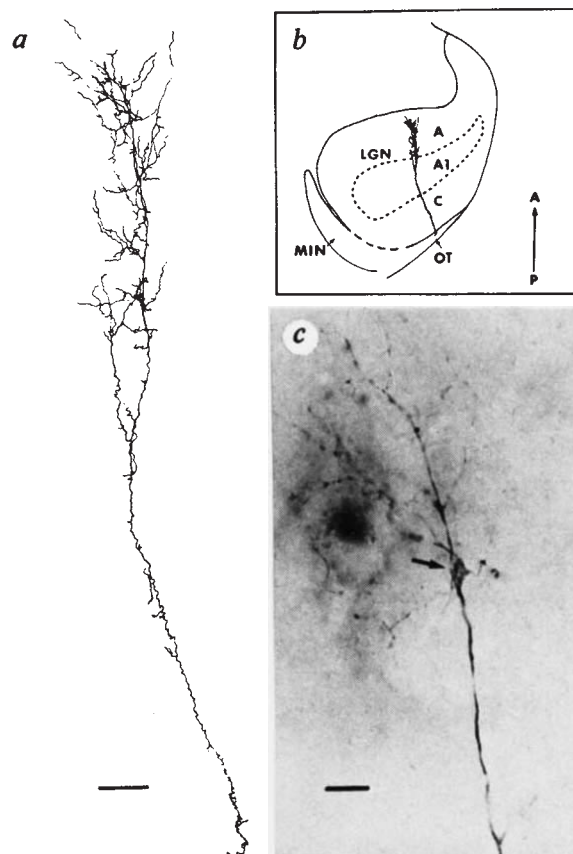


Fig. 1 An HRP-filled retinogeniculate axon from E55 preparation to illustrate several typical morphological features seen at this age. *a*, Camera lucida reconstruction of the axon made from six serial sections as it leaves the optic tract and traverses the LGN. Scale bar, 50 µm. *b*, The location of this axon within the LGN. The approximate location of future layers A, A1 and C-complex are indicated. Note that the major zone of arborization is within future layer A. OT, optic tract, MIN, medial interlaminar nucleus, A, anterior, P, posterior. *c*, The most distal HRP-filled processes shown in standard bright-field optics at high magnification. Arrow indicates web-like region frequently seen at branch points. Scale bar, 10 µm.

reconstructed from serial sections by means of camera lucida drawings. Axons of extremely fine calibre (0.1 µm) are routinely filled and these can be traced reliably to where they end either abruptly or in a growth cone like swelling. These observations suggest that the method used here fills axons in their entirety, although of course we can never be completely certain. Reconstructions of 104 axons were made from 15 fetuses between embryonic day 37 (E37) (before the onset of segregation) and E64 (near its completion), and from two neonatal kittens. (Gestation in the cat is 65 days.) We have examined primarily axons whose major zone of arborization is within the region of the LGN destined to contain layers A and A1.

Figure 1 shows a typical example of an HRP-filled axon from an E55 preparation. The entire axon as reconstructed from six serial sections is shown in Fig. 1*a*; its location within the LGN is shown in Fig. 1*b*. The axon leaves the optic tract and traverses about halfway across the nucleus before it begins to ramify. Previous studies^{9,11} have shown that the territory closest to the innermost border of the nucleus (furthest from the optic tract) is occupied exclusively by afferents from the contralateral eye throughout development; this territory is part of future layer A. Afferents from the ipsilateral eye never reach this innermost border, although the two sets of afferents do overlap each other everywhere else. In view of the location of its terminal arbor, we consider it most likely that this axon originates from the contralateral eye. Within the LGN, the arbor is restricted primarily to the distal half of the axon and is roughly cylindrical in shape: about 50–100 µm wide and 450 µm long. The proximal

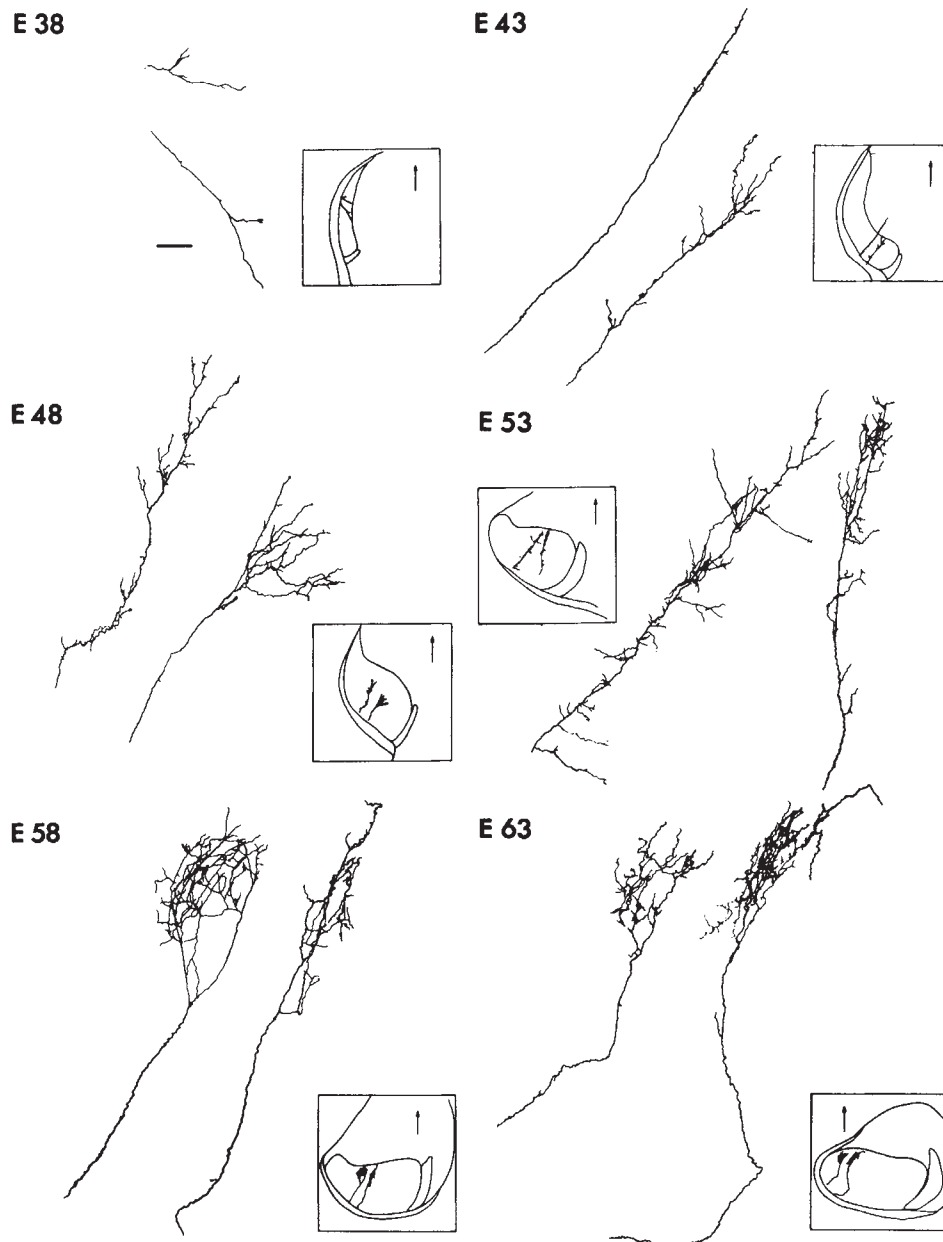


Fig. 2 Reconstructions of axons from six separate fetal ages: E38, E43, E48, E53, E58 and E63. At each age, two representative axons were chosen to illustrate the extremes in morphology. Insets accompanying each pair of axons show the location of the axons within the LGN as viewed in horizontal section. Arrows in each inset point in the anterior direction; medial is to the right, lateral to the left. All axons are drawn to the same scale (scale bar, 50 μ m). Note gradual increase in complexity of arborization with age and presence of fine side branches along main axon trunk at E48 and E53.

half as it courses through ipsilateral eye territory is smooth, with only occasional short delicate side branches that sometimes end in swellings. The appearance of the most distal portion of the axon as viewed in bright-field optics is shown in Fig. 1c to illustrate the fineness and complexity of the branching pattern at this age. Web-like structures such as the one indicated in the middle of the field (arrow) are frequently found at axonal branch points.

The progressive changes in morphology that occur during development are illustrated in Fig. 2, in which a representative selection of retinogeniculate axons within the LGN at six fetal ages between E38 and E63 have been drawn to the same scale to facilitate comparison. It is between these fetal ages that the two sets of retinogeniculate afferents undergo the change from an initial partially overlapped to a segregated state. At each age, the two axons with the simplest and the most complex morphology are illustrated. These extremes may reflect the

differential arrival and maturation of axons from retinal ganglion cells born at different times^{15,16} or in the older fetuses, axons from different classes of retinal ganglion cells.

At E38, axons have entered the nucleus and are extremely simple in morphology. Each axon has a delicate major trunk with one or two short side twigs. Even at this early age some axons traverse the entire extent of the nucleus, as shown in the upper left E38 inset of Fig. 2. At this and all other ages examined, axons exit from the optic tract in an orthogonal trajectory to enter the nucleus. At E43, the afferents elongate further and acquire a number of side branches along the main trunk. At the distal end, often several long processes are grouped together to form what can be identified for the first time as a simple terminal arbor. Occasionally, axons also traverse the nucleus to extend beyond its medial border, as is shown in the E43 inset. The distal portion of these axons is located in a region that contains late-generated migrating neurones en route to the LGN^{9,17}.

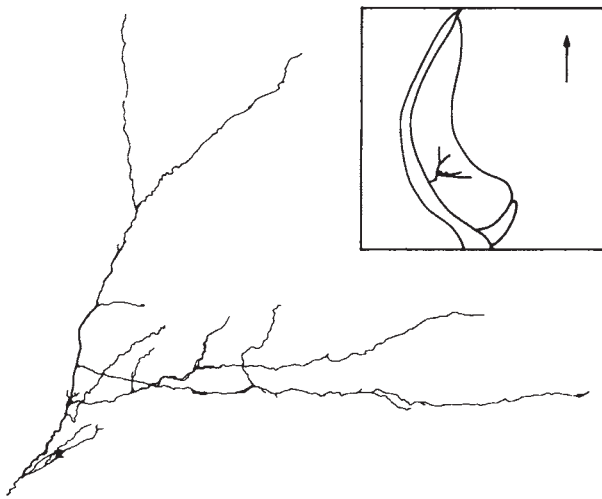


Fig. 3 An axon reconstructed from an E43 preparation to illustrate the unusually unrestricted lateral extent of its arborization. Axons with such arbors were rare at every age, and this figure illustrates the most extreme example encountered in this study. Inset shows location of axon within the LGN. Scale bar, 50 μ m.

During the next 5 days, the nucleus enlarges due to the arrival of migrating cells and begins to undergo a displacement in the horizontal plane that is not complete until birth⁹. At the same time, as additional axons from the two eyes invade the LGN, overlap between the two sets of afferents reaches a maximum (see ref. 9, Fig. 13). In view of the extensive overlap present, many axons could have correspondingly widespread arborizations along the whole length of their trajectory across the nucleus. However, axons examined at E48 did not arborize in this manner (Fig. 2). Rather, with the exception of a few short side twigs, branching was restricted to a simple terminal arborization. In addition, although more extensive than those seen at earlier ages, the terminal arbors were nevertheless restricted in width (in the plane of the layers) to 150–200 μ m. This restriction in width was seen at every age studied with only four exceptions (2/28 axons at E43 and 2/14 axons at E48). In each of these, the collaterals that issued from the main axon trunk were simple but extended laterally to occupy a territory $\sim$ 300 μ m across. A reconstruction of the most laterally branched axon encountered in this study is shown in Fig. 3.

At E53, when overlap between the two sets of afferents is still present, the pattern of arborization is more elaborate. In Fig. 2 side branches protrude from the main axon trunk everywhere giving the axon a hairy appearance. Since the two axons illustrated traverse the entire nucleus, suggesting that they originate from the contralateral eye, some of their side branches must also be located within ipsilateral eye territory. For the first time, the terminal arborization of many axons appears cylindrical in shape. This appearance is even more pronounced by E58, when the familiar laminar pattern of eye input can be recognized. Virtually all axons studied at this age have a clearly defined and extensive terminal arborization (Fig. 2). However, the main axon trunk is smooth and almost devoid of the side branches that were so characteristic just 5 days earlier. These morphological changes seen between E53 and E58 are consistent with the suggestion that the reduction in overlap leading to the segregated state is at least in part due to the retraction of the short side branches concurrent with the elaboration of an extensive terminal arborization on the same axon.

By E63, only small zones of overlap remain between the two sets of afferents along the interlaminar borders⁹. Accordingly, the terminal arborizations of individual axons are restricted chiefly to the LGN regions known to receive innervation from either the contralateral or the ipsilateral eye. The overall morphology of the axons at E63 resembles that at E58 but the terminal arbor is further refined and elaborated into a plexus

of branches with swellings and varicosities on the finer processes similar to those seen in the immediate postnatal period¹⁸.

These observations show that between E38 and E63, retinogeniculate axons undergo a progressive transformation from a simple, unbranched state to one in which the basic framework of the terminal arbor is established relatively early during prenatal development. Subsequently, a good deal of further growth and maturation occurs within this axonal framework so that relatively complex arbors are found by birth. However, for the adult pattern of arborization to occur^{19,20}, this growth continues during postnatal life as has been shown in recent studies.^{18,21,22}

A major question considered here is whether the reduction in overlap of the two sets of afferents is accompanied, at the level of individual retinogeniculate axons, by a retraction of widespread arborizations across the nucleus. Widespread branching followed by major retraction was not seen in our material. On the contrary, during the period of overlap, retinogeniculate arbors are relatively simple and the major morphological correlates of the segregation process found in the present study consist of the loss of the fine hairy side branches along the length of the main axon and the further elaboration of the remaining terminal arborizations to give rise to the segregated laminar pattern of eye input. Thus, the developmental events leading from an initially intermixed state to the adult pattern of connectivity need not involve a large-scale retraction of widespread axon arbors.

Physiological evidence indicates that during the period of overlap individual LGN neurones situated within zones of ipsilateral input also receive functional synapses from the contralateral eye¹¹. It would be very interesting to know whether the side branches given off by contralateral axons coursing through this ipsilateral zone are indeed the source of these functional synapses. Anatomical studies also indicate that during this developmental period, a substantial loss of retinal ganglion cell axons occurs within the optic nerve^{23–25}. Although this loss of ganglion cell axons could contribute to the reduction in overlap between retinogeniculate afferents, our present results demonstrate that axonal growth and retraction must also have a major role in producing the laminated pattern of eye input.

The course that individual axons take during this developmental period also has implications for the degree of topographic order present within the LGN. In the adult retinogeniculate system, afferents from the two eyes terminate in distinct layers, each layer containing a complete map of the visual hemifield from one eye. The position of each retinogeniculate axon within a given LGN layer is therefore defined according both to its eye of origin and to the topographic map. In our material, the overwhelming majority of axons traverse the nucleus in straight trajectories aligned with the known lines of projection of the visual field in the adult LGN²⁶, with very little lateral branching in the orthogonal direction (within the plane of the layers). This observation suggests that even as early as E38 a significant degree of topographic order may be present in the retinal projection within the LGN. Order may even be present within the optic tract itself during fetal development^{15,27}. These considerations raise the possibility that axons from the two eyes may grow into the nucleus in approximate topographic register. If so, an axon from one eye need only segregate from its nearby topographic counterpart from the other eye to achieve the adult-like pattern of connectivity in which inputs from the two eyes are not only topographically in register, but also segregated from each other. Such a scenario suggests that the manner in which individual retinogeniculate axons establish their final pattern of connectivity within the LGN involves an economy of axonal growth and development.

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Real-time optical imaging of naturally evoked electrical activity in intact frog brain

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A major obstacle to understanding the function and development of the vertebrate brain is the difficulty in monitoring dynamic patterns of electrical activity in the millisecond time domain; this has limited investigations of such phenomena as modular organization of functional units, seizure activities and spreading depression. The use of voltage-sensitive dyes^{1–6} and the recent development of the use of an array of photodiodes⁷ has provided a unique technique for monitoring the dynamic patterns of electrical activity in real time from a variety of invertebrate^{1,2,7} or vertebrate neuronal preparations^{8–10} including the rat cortex¹¹. In the present study, this technique has been used to investigate the intact optic tectum of the frog. We demonstrate that optical measurements can be used for real-time imaging of spatio-temporal patterns of neuronal responses and for identification of functional units evoked by natural visual stimuli. We report also the structure of the new voltage-sensitive probe that facilitates the *in vivo* applications of this technique.

Staining solution (0.1–0.5 mg ml⁻¹) was applied topically to the optic tectum for 20–30 min. The tectum was then rinsed with amphibian Ringer's solution for 20 min. For testing the dyes, a 50–150-ms green light was flashed through a light guide onto one eye, while fluorescence signals were recorded from the contralateral tectum. Four styryl dyes^{6,12} (out of 27 tested) yielded large optical signals that could often be detected in a single sweep. Of these four, RH-414 (4-[4'-p-diethylamino-phenylbuta-1',3'-dienyl]-γ-triethylammonium-propyl pyridinium bromide), gave the best signal-to-noise ratio. The fractional change in fluorescence, $\Delta F/F$, observed with this dye was $0.5\text{--}4 \times 10^{-3}$. The other three dyes (RH-160, RH-237 and RH-376)⁶ stained the tectum more lightly, and gave somewhat smaller signals.

The fluorescence signals evoked in the tectum by a flash of light are shown in Fig. 1a. The detected signals probably represent the activation of several different classes of excitatory retinal afferents as well as postsynaptic responses in the tec-

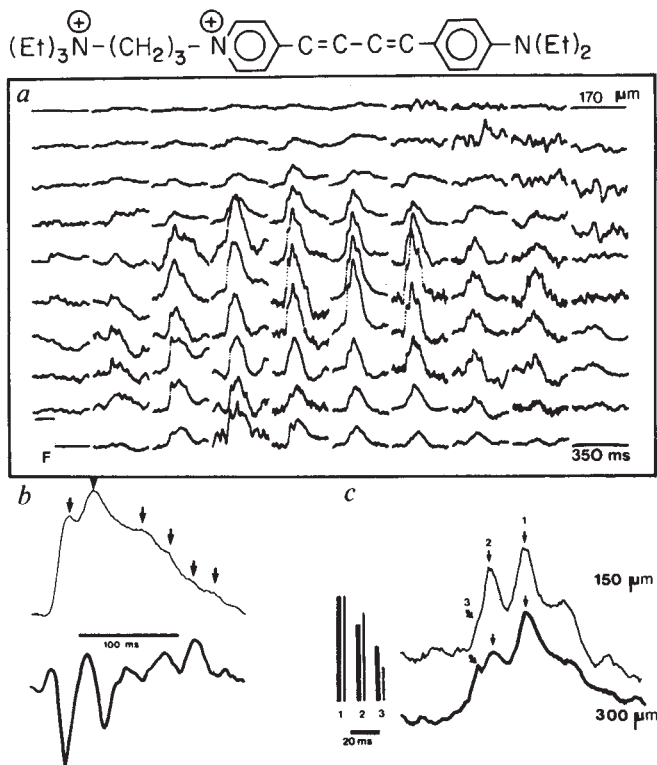
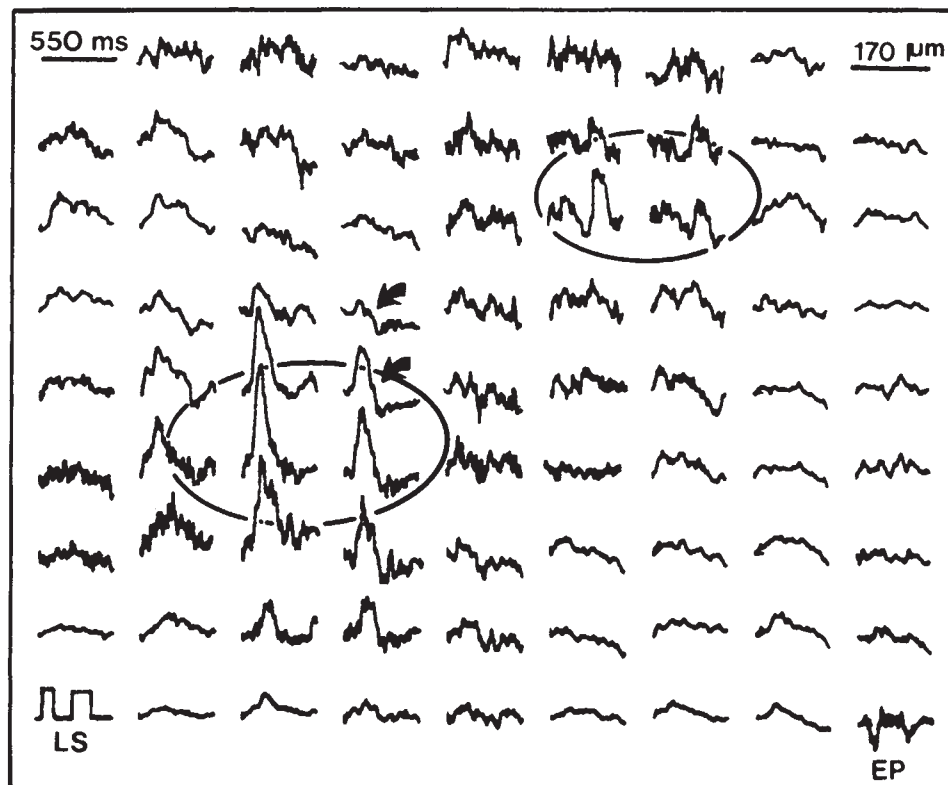


Fig. 1 *a*, Fluorescence recording of naturally evoked responses in the frog tectum. Frogs (*Rana ridibunda*) were anaesthetized by bathing them in water containing 0.5 g l^{-1} tricaine methanesulphonate (Sigma), then the dorsal lymph sac was injected with 0.1 ml tubocurarine chloride (0.7 mg ml^{-1}). A $5 \times 4 \text{ mm}$ window in the skull was cut with a rongeur, and the dura membrane was removed with fine forceps. The tectum was stained with 0.5 mg ml^{-1} RH-414 for 20 min. (The structure of RH-414 is shown at the top.) A Zeiss Universal microscope equipped with an epifluorescence illuminator and a 100 W tungsten-halogen lamp was used. The microscope $\times 10$ objective formed a real magnified image which was projected onto a 10×10 photodiode array (Centronix, London). The size of each diode was $1.4 \times 1.4 \text{ mm}$. Each element received light from an area of $170 \times 170 \mu\text{m}$ on the tectum. The output of the photodiodes was then amplified and stored in the computer memory (for more details see refs 7, 8). The output of 96 photodetectors is shown at their relative locations. Signal averaging was not used, but the data were smoothed by digital filtering. Stimulus: 150-ms light flash (shown at F) presented to the contralateral eye. Slow noise due to vascular pulsation was reduced by triggering the data collection with the peak of the electrocardiogram and subtracting the result for the trial with the stimulus from the following trial without a stimulus. *b*, Comparison of optical intracellular population recording with the electrically recorded surface evoked potential. The two recordings were $700 \mu\text{m}$ apart. A silver ball electrode ($200 \mu\text{m}$ diameter) and a high gain differential amplifier were used. Four trials were averaged. *c*, Depth of field resolution. Comparison between the output of a photodetector in two consecutive experiments at two different depths. The peak amplitudes of the two recordings were normalized. The bars at the left show the relative amplitudes of individual components of the signals recorded at a depth of $300 \mu\text{m}$ (thick trace, thick bars) and $150 \mu\text{m}$ (thin trace, thin bars). (When the experiments were repeated, identical results were obtained.) A $\times 40$ water immersion objective was used.

tum^{13,14} and possibly also glial depolarization. Figure 1b shows the correspondence between individual components of the fluorescence signal and the extracellularly recorded electrical signal. The optical and electrical signals are expected to be different because they represent the superposition of intracellular potential changes⁸ and of extracellular current flow, respectively. However, the number of resolved peaks on the two types of recording is similar. (More complex visual stimuli, such as moving bars or annuli, evoked very complex spatio-temporal patterns of activity with up to 14 resolved peaks on many of the fluorescence signals.)

Fig. 2 Retino-tectal mapping by real-time imaging of neuronal activity. Same experimental conditions as for Fig. 1a. A 100-ms, 2-mm diameter light spot was focused on the centre of a Tektronix 604 oscilloscope screen positioned approximately along the eye's optic axis (17 cm away). The microscope field of view was adjusted until signals were detected (on two to four photodetectors) at the centre of the microscope field (not shown). After mapping the centre of the oscilloscope on the tectum, two light spots (10 cm apart) were positioned on the screen in the time sequence shown at the bottom left-hand corner (LS). Fluorescence signals from 9×9 photodetectors are shown. The largest signals ($\Delta F/F = 2 \times 10^{-4} - 5 \times 10^{-4}$) were obtained in two well defined loci. The timing of each corresponds to the distinct light spot stimulus. Twenty trials were averaged. Focus depth: 300 μm below the surface. The bottom right-hand corner shows the evoked potential ball electrode recording from the centre of the field (EP), performed after the optical experiments. It also shows that the amplitude of the second response is smaller as observed optically. (Electrical recordings from five unstained preparations indicated that the activity in the second focus was always smaller. The origin of this long-range 'inhibition' has not yet been investigated.) For visualization of the spatio-temporal pattern of the evoked responses, we used a display processor⁸. The selected two video frames at the bottom of the figure show the activity at two different times corresponding to the peak activity of each focus. The image of the preparation was omitted for clarity and is shown at the bottom left: ON, optic nerve; T, tectum. Four experiments gave identical results. When the stimulation sequence was reversed, a similar result was obtained but the latency of the corresponding signals was reversed also. Individual spots on the screen also evoked activity at the appropriate locus.



A striking structural feature of the amphibian optic tectum is its laminar organization, which has facilitated laminar current source-density analysis^{14,15}. As shown in Fig. 1c, the optically recorded response also varies with depth, as determined by simply changing the focal plane of the microscope. The origin of the shortest latency component appears to be deeper than the source of the second component, in agreement with the fact that retinal afferents having fast-conducting myelinated axons, terminate deeper than the slow-conducting non-myelinated axons¹³. Thus, a laminar analysis of neuronal activity can be performed optically with a coarse resolution. Conventional microscopes do not provide good resolution of images in a thick preparation, thus the three-dimensional resolution of the optical signals is hampered also^{10,16,17}. However, there are several optical and mathematical means to achieve considerable improvement in the three-dimensional resolution of the optical technique; their implementation is discussed elsewhere^{17,18}.

The retino-tectal connections possess a high degree of topographical order¹⁹, and a given stimulus in a portion of the field of view of the retina evokes a focus of excitation in a restricted area of the tectum. We tested the sensitivity and spatial resolution of the technique by presenting discrete and weak stimuli (that is, dim spots of light on a dark background) to different parts of the visual field. In the experiments illustrated in Fig. 2, a stationary light spot (2 mm diameter, 0.6° visual angle, 100 ms duration) was first presented to the temporal visual field of the right eye, and 210 ms later it was presented at a location

10 cm more nasally (a displacement of 26° of visual angle on the retina). This displacement corresponds to a displacement in the focus of activity on the tectum of $\sim 500 \mu\text{m}$ (ref. 19). As shown in the upper part of Fig. 2 (circled areas), this sequence of stimulation did in fact produce two localized sets of excitatory foci, separated by $\sim 500 \mu\text{m}$. The largest peaks in excitatory foci were recorded over an area measuring $\sim 340 \mu\text{m} \times 340 \mu\text{m}$. Because the size of a single terminal arborization of a retinal afferent has a diameter of $100-300 \mu\text{m}$ ^{20,21}, this result suggests that the visual stimuli activated retinal ganglion cells which terminate in a restricted region, and then excited mostly a small vertical column of tectal neurones. (However, smaller signals, of unidentified origin(s), were distributed over a large area of the tectum.)

Anatomical investigations of intertectal connections²⁰ suggest that focal tectal excitation may spread over the whole tectum, but pretectal and intratectal inhibition shapes the size of the excited vertical column. Therefore, inhibition should be detected at the border of the column. In five experiments we observed a negative-going deflection on the 'intracellular' optical records which followed the excitatory response and this was most prominent in the medial-rostral side of the column (Fig. 2). Topical application of 1 mM bicuculline (a blocker of some inhibitory synapses) led to a considerable increase (up to 10-fold) in the area of excitation, suggesting that part of the negative-going responses may represent the proposed²⁰ inhibitory synaptic potentials. (Recurrent inhibitory potentials with a similar time

course have been recorded recently in the tectum *in vivo*²² and *in vitro*²³ by intracellular recording.)

Our results establish that optical signals can be readily recorded from the intact frog brain in response to physiologically relevant stimuli. Further, the 'intracellular population activity'⁸ recorded optically is localized to its regions of origin, unlike extracellular field potentials, which may spread over variable distances determined by the flow of extracellular current. However, there are also difficulties that warrant discussion. Some pharmacological side effects may be expected wherever extrinsic probes are used^{2,7,17}. With the four dyes we selected, the electrically recorded, visually evoked potential was similar before and after the staining, only if a low dye concentration was used. (Optical signals could be recorded at least 4 h after staining.) The measurement is also quite sensitive to minor movements caused by pulsation or blood flow under the pigmented pia mater. In preliminary experiments, this type of noise was totally eliminated by perfusing the frog with a laminar flow

of saline through the aorta. Further improvements of these difficulties have been discussed elsewhere^{10,17,18}.

The advantages of the optical technique are first that it provides real-time imaging of the 'intracellular' population activity at many loci simultaneously. Further improvements should facilitate three-dimensional imaging of the activity from the entire depth of the tectum (~600 μ m). Second, the present method has a major advantage over the 2-deoxyglucose method²⁴ in that it permits many experiments to be carried out on the same live preparation. This technique has already been applied successfully to the investigation of the rat somatosensory cortex (ref. 25 and H. S. Orbach, L. B. Cohen and A.G., manuscript in preparation).

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Common non-hormone binding component in non-transformed chick oviduct receptors of four steroid hormones

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Steroid hormones produce a response in target cells by binding to hormone-specific soluble receptors, which undergo a conformational change, leading to their interaction with chromatin and to modified gene expression. In a previous paper¹, we described a monoclonal antibody, BF₄, that specifically recognizes and binds the non-transformed '8S' form of chicken oviduct progesterone receptor (8S-PR). We now show that BF₄ does not form an immune complex with the 4S transformed form of ³H-progesterin-labelled progesterone receptor, but does interact with the 8S non-transformed forms of the oestrogen, androgen and glucocorticosteroid receptors. Our results suggest that the antigenic determinant recognized by BF₄ is present on a non-hormone binding unit, which we identify as a polypeptide of molecular weight (MW) 90,000 in the case of the progesterone receptor, and that this unit is common to other 8S non-transformed chicken steroid receptors.

BF₄ was obtained after fusion of rat spleen cells, immunized with partially purified molybdate-stabilized 8S-PR, with mouse myeloma cells Sp2/0-Ag14 (ref. 1). We demonstrated its specific interaction with the molybdate-stabilized, non-transformed 8S-PR in chick oviduct cytosol by ultracentrifugation analysis. In the presence of an excess of BF₄, the 8S ³H-progesterin binding receptor sedimented at 10–11S, while after incubation with an excess of PR, the ³⁵S-methionine labelled BF₄ (³⁵S-BF₄) peak was changed from ~7S to ~10S¹.

We examined the interactions between BF₄ and PR after various stages of the two receptor purification procedures used (see Table 1, a and b). In the first procedure (Table 1, a), non-transformed 8S-PR was purified by affinity chromatography in the presence of molybdate, and labelled with ³H-progesterin². Its sedimentation coefficient shifted to 10S in 10–35% glycerol gradient ultracentrifugation following incubation with excess BF₄ (Fig. 1a); after exposure to an excess of PR, ³⁵S-BF₄ was also recovered in the 9–10S region (Fig. 1b). When the affinity gel eluate containing non-transformed 8S receptor labelled with ³H-hormone was subsequently passed through a DEAE-Sephacel column in the absence of molybdate, ³H-P-PR was eluted as a major peak at 0.25 M KCl. When this peak was incubated with an excess of BF₄, no displacement of tritium was observed, the bound tritiated ligand remaining 4S (Fig. 1a). However, when ³⁵S-BF₄ was incubated with an excess of the 0.25 M KCl eluate, the ³⁵S-peak of the antibody was displaced from 7S to ~9–10S (Fig. 1b). These results suggested the presence of a non-ligand binding component in the non-transformed 8S-PR structure.

During the second purification procedure (Table 1b), experiments were performed with crude cytosol in which PR was transformed by exposure to high salt concentration³. Crude cytosol prepared in the absence of molybdate was precipitated with 30% ammonium sulphate, labelled with ³H-progesterin and incubated with excess BF₄ or with a trace amount of ³⁵S-BF₄. Again, the peak of ³⁵S radioactivity was found in the ~9S region, while the receptor-bound ³H-steroid peak remained 4S (Fig. 2a). Addition of a large amount of unlabelled BF₄ to the incubation medium did not affect the 4S sedimentation coefficient of the bound tritiated progesterin; the 9S ³⁵S-peak was abolished and the ³⁵S-radioactivity was recovered in the 7S region of the gradient (Fig. 2a). We checked that salt-induced transformation did not decrease the binding of ³H-hormone to the receptor, and then excluded the possibility of a preferential interaction of BF₄ with receptor having lost the ability to bind hormone. Finally, when the salt-transformed cytosol preparation was directly loaded onto the affinity column, the ³H-progesterin-labelled eluate did not form any immune complex with BF₄ (unlabelled or ³⁵S) (Fig. 2b).

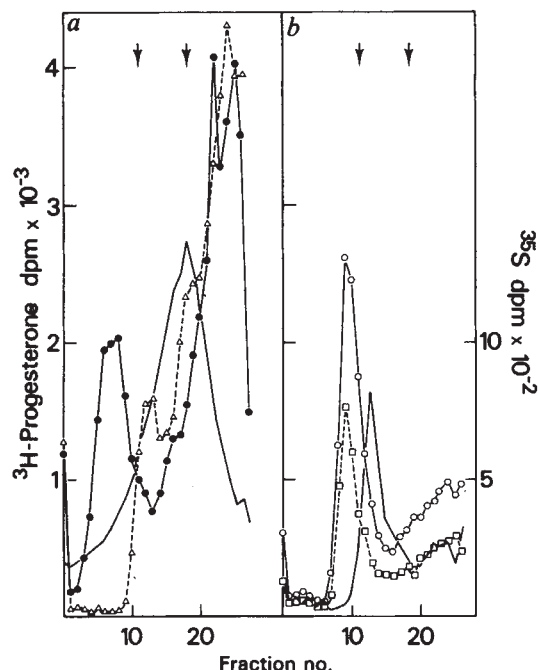


Fig. 1 Density gradient sedimentation analysis of complexes of (anti-chick oviduct PR) BF_4 monoclonal antibody with purified chick oviduct PR. Samples of 0.2 pmol of ^3H -P-labelled affinity chromatography eluate (see below) were incubated with 200 μl BF_4 (●—●), control myeloma cell culture medium (Δ — Δ) (a) or 25 μl ^{35}S - BF_4 (○—○) (b); 1 pmol of 4S-PR-containing DEAE-Sephacel eluate was incubated with 10 μl ^{35}S - BF_4 (□—□) (b). a, The ~4S sedimentation profile (—) of 0.15 pmol of identically ^3H -P labelled, 0.25 M KCl DEAE-Sephacel eluate, obtained in a parallel experiment, incubated with 200 μl BF_4 -containing ascitic fluid or control myeloma cell culture medium (not shown); both control and BF_4 -exposed samples gave an identical 4S peak. b, Sedimentation profile of ^{35}S - BF_4 alone (—). Arrows indicate the sedimentation position of the internal standards. Sedimentation was from right to left. Other controls were carried out with unrelated rat immunoglobulin (as in experiment of Fig. 4, PR2).

Methods: Cytosol prepared in TE-Mo (10 mM Tris, 1.5 mM EDTA, 10% (v/v) glycerol, 12 mM 1-thioglycerol, 20 mM Na_2MoO_4 , pH 7.4 at 25°C) was loaded onto the NADAc-Sephacel affinity gel². Receptor was eluted with 2 μM of the high-affinity progesterin ^3H -ORG 2058 (specific activity 1.6 Ci per mmol) (Amersham) and further incubated with 100 nM ^3H -progesterone (P) (specific activity 89 Ci per mmol) for 30 min at room temperature and 40 min at 4°C. Excess unbound steroid was removed by incubation with a charcoal (0.5%) dextran (0.05%) suspension in TE-Mo, containing 2 mg gelatin per ml, and centrifugation at 1,500g for 5 min. The affinity chromatography eluate was further purified by DEAE-Sephacel chromatography. In the absence of molybdate, the 4S-transformed labelled receptor was eluted mostly at 0.25 M KCl and incubated with 100 nM ^3H -P (specific activity 89 Ci per mmol) overnight at 4°C and for 30 min at room temperature. Excess unbound steroid was removed as described above. Samples containing purified ^3H -P-PR were incubated with BF_4 monoclonal antibody, control myeloma cell culture medium (both partially purified by 50% ammonium sulphate precipitation followed by DEAE-cellulose chromatography), or ^{35}S -methionine-labelled BF_4 (ref. 1) for 5 h in a final volume of 300 μl . Two hundred and fifty μl were layered on top of 10–35% glycerol gradients and run for 17 h at 220,000g in a SW 60 rotor (Beckman). Sedimentation coefficients were determined according to Martin and Ames¹⁵ using horseradish peroxidase (Sigma, type VI) (3.6S) and fungal glucose oxidase (Boehringer, Mannheim) (7.9S) as internal standards.

Altogether, these data (summarized in Table 1) show heterogeneity in PR subunits and/or molecular species and suggest that the transformation process is accompanied by dissociation of the receptor into two kinds of components: one binds the hormone, can be purified by affinity chromatography and does not form any detectable complex with BF_4 (refs 4 and 5); the other is a non-progesterin binding component that is

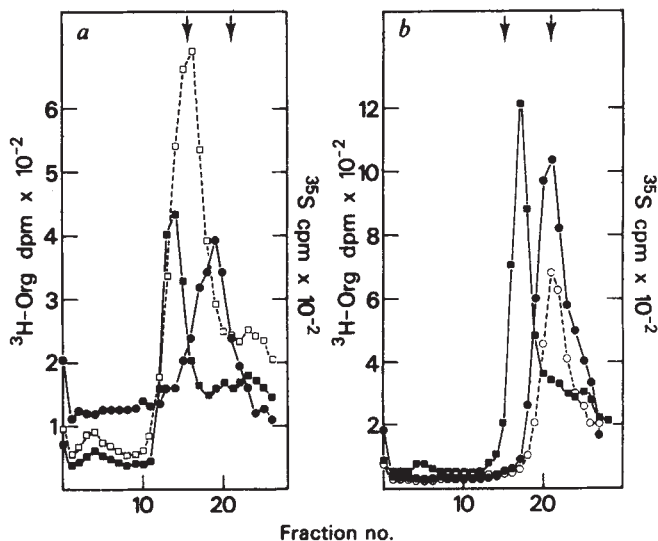
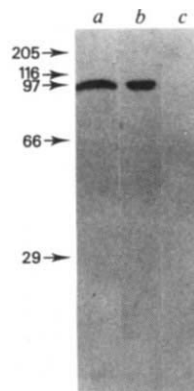


Fig. 2 Density gradient sedimentation analysis of salt-transformed PR after incubation with BF_4 monoclonal antibody.

Methods: Cytosol was prepared in the absence of molybdate. a, The 30% ammonium sulphate precipitate was labelled with ^3H -ORG 2058 (specific activity 42 Ci mmol^{-1}). Samples were incubated with 200 μl BF_4 crude ascitic fluid (●—●) and with control myeloma cell culture medium (not shown); the two profiles were superimposable; the samples were also incubated with ^{35}S - BF_4 in the absence (■—■) or presence (□—□) of 200 μl of ascitic fluid. b, Cytosol was treated with 0.3 M KCl and loaded onto NADAc column². Elution was performed with 2 μM ^3H -ORG 2058 (specific activity 14 Ci mmol^{-1}). 0.2 pmol of ^3H -ORG-PR affinity chromatography eluate were incubated with 20 μl ascitic fluid (●—●) or control myeloma cell culture medium (○—○); 10 μl of ^{35}S - BF_4 was centrifuged alone (not shown) or after incubation with 1.5 pmol of the affinity chromatography eluate (■—■); identical profiles were obtained. In both cases incubations were performed at 0°C for 5 h in a final volume of 250 μl . Two hundred μl were layered onto a 5–20% sucrose gradient (a) or 10–35% glycerol gradient (b) containing 0.3 M KCl and run as described in legend of Fig. 1.

Fig. 3 Immunoblotting of progesterone receptor with BF_4 monoclonal antibody^{16,17}. a, Total cytosol (100 μg protein). b, Purified molybdate-stabilized 8S-PR (0.5 μg). c, Affinity chromatography purified salt-transformed PR (0.75 μg) (see also ref. 4).

Methods: Electrophoresis was performed in 10% polyacrylamide slab gel according to the procedure of Laemmli¹⁸, and carried out at room temperature for 12 h at 10 mA per gel. After SDS-PAGE the proteins were transferred to nitrocellulose filters (Schleicher and Schüll BA 85). These filters were then incubated with BF_4 monoclonal antibody diluted to 1–3 μg ml^{-1} . A second ^{125}I -labelled antibody (10^2 – 10^6 c.p.m. ml^{-1}) was used to visualize the PR-antibody complexes. The filters were then placed for 3 to 20 h at -80°C with X-OMAT AR film (Kodak).



detectable by interaction with BF_4 . Both appear associated in the non-transformed 8S-PR.

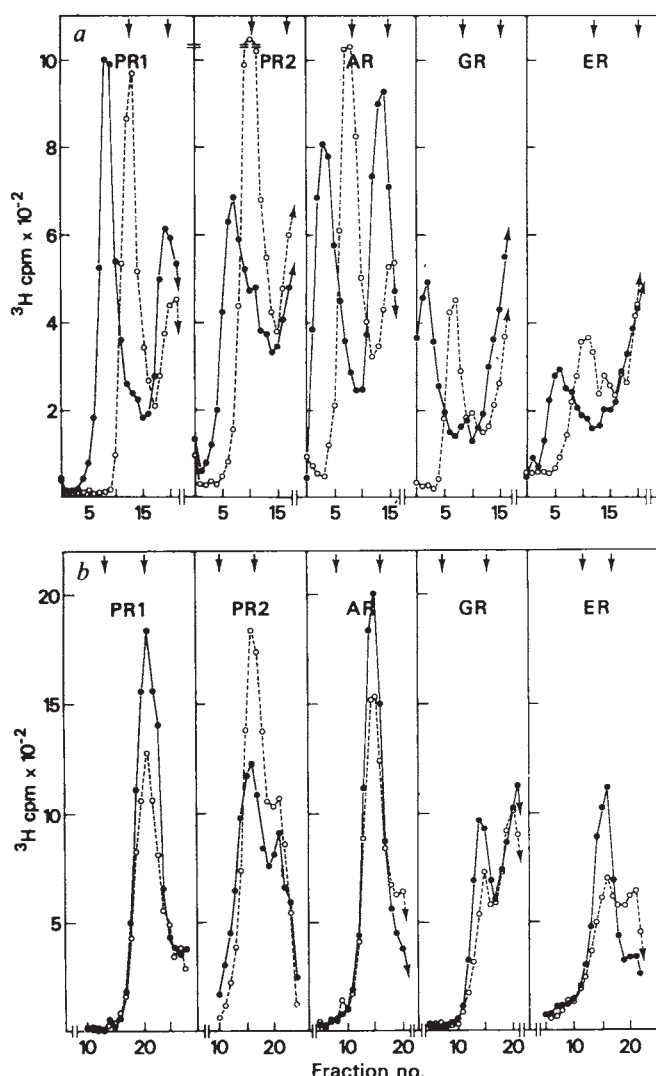
The purified 8S-PR contains a major protein, MW 90K, detectable by Coomassie blue^{2,6} and silver staining^{4,5} of SDS-PAGE slab gels (previously its MW was reported as ~85 K), and it also includes^{4,5} the 'A' (MW ~79 K) and 'B' (MW ~110 K) PR components previously described⁷. When 8S-PR

Table 1 Interaction of monoclonal antibody BF₄ with different preparations of progesterone receptor at different steps of two purification procedures

³ H-progesterin receptor	Receptor form	Immune complexes detected by displacement of		References
		³ H-ligand receptor	³⁵ S-BF ₄	
a				
I. Crude cytosol. Low salt and molybdate	8S	+	+	Fig. 4a and ref. 1
II. Bioaffinity chromatography eluate (molybdate)	8S	+	+	Fig. 1a and b
III. Ion-exchange chromatography (in absence of molybdate) 0.25 M KCl eluate	4S	—	+	Fig. 1a and b
b				
I. Crude cytosol. Low salt, no molybdate	8S	+	*	Ref. 5
II. Ammonium sulphate precipitate	4S	—	+	Fig. 2a
III. Bioaffinity chromatography eluate of high salt cytosol	4S	—	—	Fig. 2b

Immune complexes (+) were detected in ultracentrifugation analysis (as described in figures) by the shift of the sedimentation coefficient of either the ³H-progesterin receptor after incubation with an excess of unlabelled BF₄ or the ³⁵S-labelled BF₄ after exposure to an excess of PR.

(*) Not tested.

**Fig. 4** Reactivity of BF₄ monoclonal antibody with non-transformed and transformed forms of progesterone (PR), androgen (AR), glucocorticosteroid (GR) and oestrogen (ER) receptors from chick oviduct.

Methods: Cytosol containing molybdate-stabilized, non-transformed form of PR was prepared as described. Molybdate-stabilized, non-transformed forms of androgen and glucocorticosteroid receptors from cytosol prepared in TE-Mo buffer were incubated with 9 nM ³H-dihydrotestosterone (DHT) (specific activity 109 Ci mmol⁻¹) in the presence of 30 nM deoxycorticosterone (Sigma) or 40 nM ³H-dexamethasone (specific activity 89 Ci mmol⁻¹) in the presence of P 40 nM (Roussel-Uclaf) overnight at 4 °C. Both of the radioactive steroids were from Amersham, UK. Binding activities were respectively 2 nM for the AR and 10 nM for the GR as measured after removal of excess unbound steroid with the above described charcoal-dextran procedure (see legend to Fig. 1). The low salt cytosoluble fraction of chick oviduct homogenates containing non-transformed form of ER was prepared in phosphate-glycerol buffer (5 mM sodium phosphate, 10% glycerol, 1 mM dithiothreitol, 0.5 mM EDTA, 20 mM sodium molybdate, pH 7.4 at 23 °C). The transformed form was prepared in the same buffer without molybdate and treated for 30 min at 28 °C. After labelling at 0 °C for 4 h with 10 nM ³H-oestradiol (E) (specific activity 95 Ci mmol⁻¹) (Amersham) in the presence or absence of a 200-fold excess of unlabelled E (Roussel-Uclaf), specific-binding activity was 0.7 nM, as measured after exposure to dextran-coated charcoal. ³H-P (0.2 pmol), ³H-DHT (0.3 pmol) and ³H-dexamethasone (0.3 pmol) labelled receptors (PR1, AR, GR) were incubated with partially purified BF₄ monoclonal antibody from ascitic fluid or control myeloma cell culture medium (300 µl) for 5 h at 4 °C in a final volume of 500 µl. Non-transformed and transformed forms of ³H-E-ER (0.07 pmol) were incubated with BF₄ or control medium (150 µl) in a final volume of 250 µl. Two hundred µl were layered on top of 10–35% glycerol (PR) or 5–20% sucrose (other receptors) gradients in homogenization buffer and run as described above (see legend of Fig. 1). Sedimentation profile of ³H-steroid-labelled receptor in the presence of BF₄ (●—●) or control medium (○—○) in low-salt gradient containing molybdate (a) or high-salt gradient containing 0.5 M KCl (b). Another control with progesterone receptor (PR2) is shown: PR was incubated with BF₄ (●—●) or total non-immune rat IgGs (50 µg) (○—○), in control culture medium, again in low salt (a) and in high salt (b); the data were similar for AR and GR (data not shown). Bound tritiated ligand sedimenting in the 4S region of gradients shown in a can be explained either by non-specific interactions (partially decreased when cytosol was incubated with ³H-ligand in the presence of unlabelled hormone) or partial transformation of the receptors upon incubation with antibodies or during the centrifugation¹.

is subsequently chromatographed on DEAE-Sephacel in the absence of molybdate, the 0.25 M KCl peak contains both the 'B' and the 90K MW proteins⁵. Immunoblots of SDS-PAGE gels (Fig. 3) were performed with BF₄. A single band at MW 90K was visualized by the second (¹²⁵I-labelled) antibody with crude cytosol (lane a) and with the purified molybdate-stabilized 8S-PR (lane b). No band was visualized in purified PR, which had been transformed prior to the affinity chromatography step (lane c).

According to previous reports from this laboratory² and from Puri *et al.*⁶, the specific-binding activity of highly purified non-transformed molybdate-stabilized 8S-PR suggested that the 90K protein binds progesterone. Since we find by protein blotting that the 90K peptide is BF₄ positive, the most likely explanation for the contradiction is that the specific activity data reported² were in error; this may be due to imprecision in measuring proteins in very small amounts and/or to low sensitivity of Coomassie blue staining of PAGE discs. In any case several

facts argue against the possibility that the 8S-PR could be an artefact due to accidental association of the BF₄-positive 90K protein with the progesterin-binding polypeptides A and/or B in low salt, molybdate-containing medium. First, the 8S-PR is also present in cytosol prepared in the absence of molybdate, and, after incubation with BF₄, the sedimentation coefficient of PR shifted from 8 to 10S. Second, in the presence of molybdate, PR remained 8S after exposure to high salt (up to 0.75 M KCl)⁸ and urea concentration up to 2.5 M⁹. Finally, when molybdate-containing cytosol was incubated with 2 μ M progesterone prior to the affinity chromatography step, no 90K protein (and neither of course the A and B subunits) were found in the subsequent eluate; this indicated that the presence of the 90K protein in the affinity eluate depends on 8S-PR binding to the steroidal ligand of the affinity matrix⁵. In summary, even if available data do not yet permit the determination of the stoichiometry between hormone-binding and non-binding components, the results indicate that the PR in its non-transformed 8S form contains at least one hormone binding unit (A and/or B) and one non-progesterone binding component (BF₄-positive-90K).

Finally we studied the interaction of BF₄ with other steroid receptors of the chick oviduct cytosol. Preliminary results indicated the cross-reaction of BF₄ with the glucocorticosteroid receptor in its molybdate-stabilized 8S form¹⁰. Similar results have also been obtained with androgen and oestrogen receptors, labelled with their specific hormone in the molybdate containing chick oviduct cytosol (Fig. 4a). As with PR, no interaction was detectable between BF₄ and the tritiated ligand binding 4S forms of these receptors (Fig. 4b). These findings suggest that there is a common antigenic determinant involved in the structure of several non-transformed steroid hormone receptors.

The possibility that a non-hormone binding component is involved in the non-transformed steroid receptor structure has already been suggested¹¹⁻¹⁴. Detailed understanding of steroid hormone receptor function is far from being elucidated, and the discovery of a feature common to different steroid hormone receptors may be of importance.

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Note added in proof: Recent papers^{19,20} have demonstrated the nuclear localization of oestrogen receptor in absence of hormone. We have confirmed a nuclear localization of both progesterone- and non-progesterone-binding PR subunits, as detected by specific polyclonal anti-B and monoclonal anti-90 K antibodies, both in the presence and in the absence of progesterone. The 90 K protein is also detected in the cytoplasm, the 90 K protein, but no cytoplasmic progesterone-binding subunits were found^{21,22}.

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Isolation of a feline leukaemia provirus containing the oncogene *myc* from a feline lymphosarcoma

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The molecular mechanism by which feline leukaemia virus (FeLV) induces lymphoid malignancy in domestic cats is largely unknown¹. Using the insertional activation model of *c-myc* by avian leukosis virus in the induction of bursal lymphoma in chickens^{2,3}, we have now characterized the *c-myc* locus in feline tissues and investigated the possibility that FeLV may also insert within feline *c-myc*. We used the 1.5 kilobase (kb) *Pst*I fragment of MC29 *v-myc* in Southern blot analysis to characterize the structure of the *c-myc* locus in the DNA of 31 naturally occurring feline lymphomas. Analysis of a cloned *c-myc* gene from one lymphoma demonstrated that sequences homologous to *v-myc* occupy 2.6 kb of feline DNA in which a putative intron of 0.5 kb separates sequences homologous to the 5' and 3' exons represented in avian *v-myc*^{4,5}. We also observed in the DNA of this lymphoma tumour-specific fragments homologous to *v-myc*. Characterization of these molecularly cloned *myc*-hybridizing fragments revealed the presence of at least two identical FeLV proviruses 5.5 kb in length, each containing long terminal repeats enclosing a spliced version of the feline *myc* gene.

The sequence arrangement of the feline *c-myc* locus was examined by Southern blot analysis⁶ of DNA from 25 FeLV-positive and 6 FeLV-negative pathologically characterized, naturally occurring feline lymphomas and corresponding normal tissues. Hybridization to Southern blots with a radiolabelled 1.5-kb *Pst*I fragment of cloned *v-myc* DNA⁷ revealed feline *c-myc* to be complex—comprised of a large number of DNA fragments which hybridize to *v-myc* with varying intensities (Fig. 1a). We readily identified numerous restriction enzyme polymorphisms and allelic variations, one of which is shown in both homozygous (Fig. 1a, lanes 2, 3) and heterozygous (Fig. 1a, lanes 1, 4, 5) states. Hybridization to Southern blots with the radiolabelled 3' *Pst*I-*Sal*I fragment of *v-myc*, a region which corresponds to the 3' exon of avian *c-myc*^{4,5}, demonstrates that only a single fragment in *Hind*III-, *Eco*RI-, or *Kpn*I-digested normal feline DNA contains the 3' exon of feline *c-myc* (Fig. 1b). The 5' *c-myc* exon exists on the same DNA fragment, as evidenced by hybridization to the 5' *Pst*I-*Sal*I fragment of *v-myc* (data not shown). The numerous additional fragments homologous to *v-myc* (Fig. 1a) represent sequences having homology only to the 5' *Pst*I-*Sal*I fragment of *v-myc*.

The organization of feline *c-myc* observed in 30 tumour DNAs does not differ significantly among the tumours nor from the pattern observed in unaffected tissues of the same animals (Fig. 1a). Restriction enzyme polymorphisms appear as fragments of altered molecular weight in some animals, but their appearance is not tumour-specific (data not shown). However, in the DNA from a thymic lymphoma of a single animal (cat 1110), additional fragments homologous to the 3' *v-myc* probe appear after digestion with *Eco*RI, *Hind*III or *Kpn*I which do not appear in DNA from normal kidney and spleen of the same animal (Fig. 1b). Cat 1110 was diagnosed serologically as FeLV-positive, and the tumour is observed to contain four monoclonally integrated proviruses by hybridization with a probe specific for exogenous FeLV (ref. 8 and Fig. 1c).

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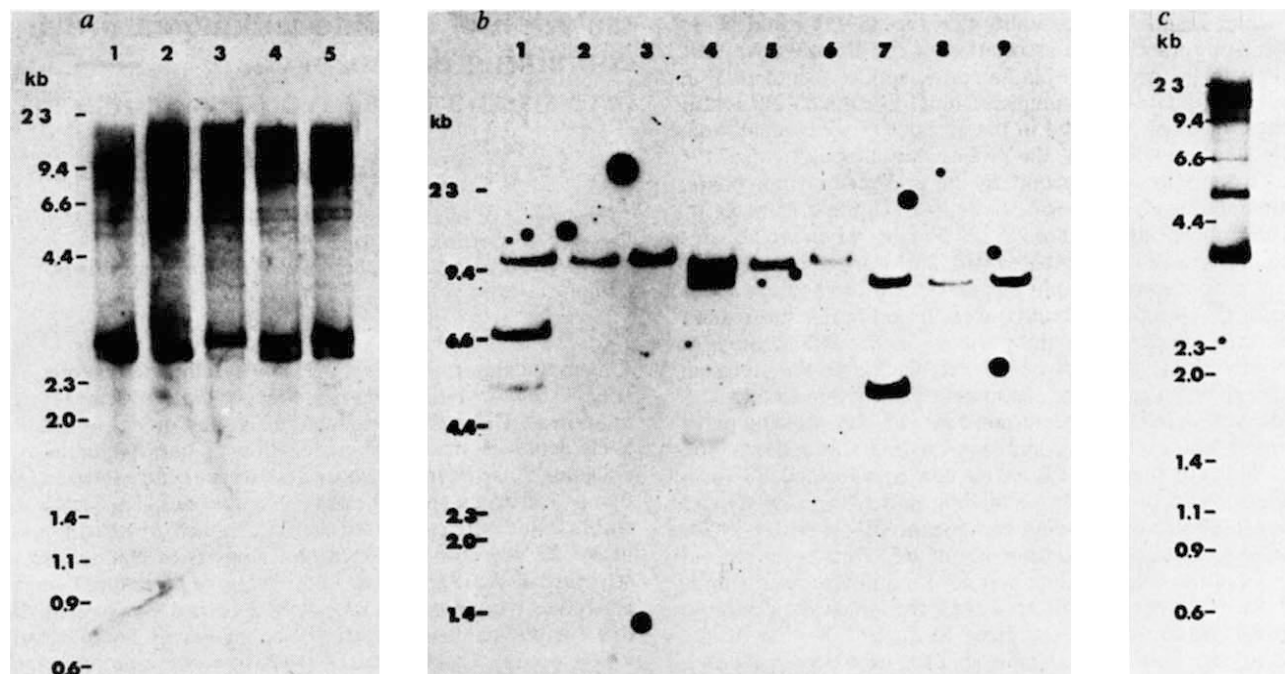


Fig. 1 Identification of sequences homologous to *v-myc* (a, b) or to FeLV (c) in DNA from tumour and normal feline tissues examined by Southern blot analysis⁶.

Methods: High molecular weight feline DNA (5 µg) was digested with the indicated restriction endonuclease, fractionated on a 1% agarose gel and transferred to nitrocellulose paper. The filters were hybridized with ³²P-labelled probes ($1-2 \times 10^8$ c.p.m. µg⁻¹) and washed as described previously⁸. Hybridization signals were visualized by autoradiography for 3 days at -80 °C using Kodak XRP film with 1 Dupont Cronex Lightning-Plus intensifying screen. Molecular length standards, a *Hind*III digest of λ DNA and a *Hae*III digest of X174 DNA, were electrophoresed in parallel and are indicated in kilobase pairs (kb). a, DNA samples from a normal kidney, cat 942 (lane 1), a normal mesenteric lymph node, cat 1103 (lane 2), a tumorous mesenteric lymph node, cat 1100 (lane 3), a tumorous mesenteric lymph node, cat 1465 (lane 4), and a normal mesenteric lymph node, cat 1005 (lane 5), were digested with the restriction endonuclease *Eco*RI and hybridized to the radiolabelled *Pst*I fragment of molecularly cloned *v-myc* (ref. 7). b, DNA samples from a thymic lymphoma (lanes 1, 4, 7), uninvolved spleen (lanes 2, 5, 8), and uninvolved kidney (lanes 3, 6, 9) of cat 1110 were digested with the restriction endonucleases *Hind*III (lanes 1-3), *Eco*RI (lanes 4-6), or *Kpn*I (lanes 7-9) and hybridized to the radiolabelled 3' *Pst*I-*Sal*I fragment of molecularly cloned *v-myc* (ref. 7). c, DNA from a thymic lymphoma of cat 1110 was digested with the restriction endonuclease *Kpn*I and hybridized to the radiolabelled FeLV-U3 probe specific for horizontally acquired FeLV (ref. 8).

We wished to characterize in detail the normal *c-myc* locus and the additional tumour-specific fragments which hybridize to *myc* in cat 1110. To accomplish this, tumour 1110 DNA was cloned in the bacteriophage vector, EMBL4 (ref. 9). We used the radiolabelled 3' *v-myc* probe to screen eight genome equivalents (1.5×10^6 recombinants) by *in situ* plaque hybridization¹⁰. Eighteen recombinants containing feline DNA inserts homologous to 3' *v-myc* were identified. Examination of these by *in situ* plaque hybridization¹⁰ using the FeLV-U3 probe, specific for exogenously acquired FeLV (ref. 8), revealed that nine recombinants also contain sequences homologous to FeLV. Three clones containing both FeLV and *myc* homology and four clones with only *myc* homology were amplified individually for detailed analysis.

Restriction enzyme mapping of a recombinant with only *myc* homology (Fig. 2a) localizes feline *c-myc* to a 2.6-kb *Eco*RI-*Sac*I fragment in which the sequences homologous to the 5' and 3' exons of avian *c-myc*^{4,5} are separated in feline DNA by a 0.5-kb *Bam*HI-*Kpn*I fragment. Southern blot analysis of normal feline DNA digested with *Bam*HI or *Sac*I (data not shown) demonstrates that fragments homologous to the 5' and 3' *v-myc* probes are of the sizes predicted by the map of feline *c-myc*.

Restriction enzyme site mapping of recombinants containing homology to *myc* and FeLV demonstrates that a 5-kb *Kpn*I fragment contains sequences homologous to both probes (Fig. 2b). Further, hybridization with the FeLV-U3 probe⁸ and a probe specific for the entire FeLV long terminal repeat (LTR)⁸ identifies at both ends of the 5-kb fragment an LTR which contains a recognition site for *Kpn*I. Thus, the sequences homologous to *v-myc* in these recombinants are localized within a provirus defined by FeLV LTRs.

Recognition sites for the restriction enzymes *Kpn*I, *Hind*III, *Eco*RI, *Bam*HI, *Sac*I and *Sal*I were positioned in two recombinants containing complete *myc*-FeLV proviruses (Fig. 2b; λ107, λ115) and in a recombinant containing a provirus truncated in cloning (Fig. 2b; λ103). The additional *myc*-hybridizing fragments apparent on Southern blots of tumour 1110 DNA, when digested with these enzymes (Fig. 1b), are of the sizes predicted by the restriction enzyme site maps shown (Fig. 2b). The 5-kb *Kpn*I fragment in tumour DNA (Fig. 1b, lane 7) represents the length of the defective provirus, which contains recognition sites for *Kpn*I in the LTR, but not internally (Fig. 2b, λ107). Digestion of tumour DNA with *Hind*III yields two additional *myc*-hybridizing fragments of 5.4 kb and 6.9 kb (Fig. 1b, lane 1) which can be accounted for in recombinants λ115 and λ107, respectively (Fig. 2b). Tumour-specific *myc* hybridizing fragments revealed by digestion with *Bam*HI measure 15 kb and 8.6 kb (data not shown), which can be accounted for by λ107 and λ115 (Fig. 2b). A single anomalous *Sac*I fragment, 7 kb in length, appears in tumour DNA (data not shown) and also in λ107 (Fig. 2b). However, λ115 contains a *Sac*I fragment homologous to *myc* of length 5.4 kb (Fig. 2b) which is not observed as tumour-specific because it co-migrates with a normal *c-myc* fragment (Fig. 2a). Digestion of tumour 1110 DNA with *Eco*RI generates a fragment 4.2 kb in length (Fig. 1b, lane 4), which appears in recombinants λ107 and λ115 (Fig. 2b). Fragments of sizes 9 and 12 kb appear in tumour DNA digested with *Eco*RI whereas a single fragment of 11 kb appears in this size range in DNA from uninvolved tissues (Fig. 1b, lanes 5, 6). The nature of the event which results in two fragments of this size in tumour DNA is under investigation.

Comparison of the restriction enzyme sites in the sequences flanking the proviruses contained in λ107 and λ115 demon-

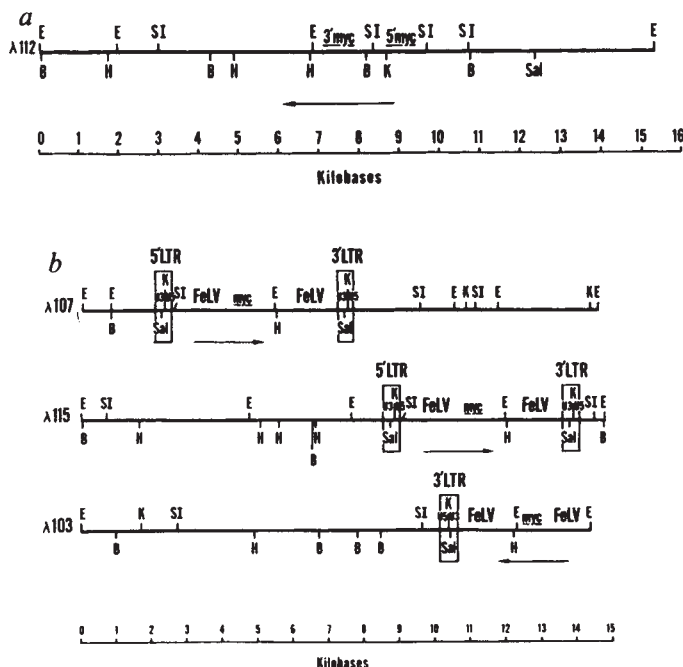


Fig. 2 Structure of recombinant phage clones containing feline *c-myc* (a) or *myc-FeLV* provirus (b). Total DNA from a FeLV-infected thymic lymphoma (cat 1110) was partially digested with *Mbo*I, size fractionated, ligated into *Bam*HI-digested EMBL4 (ref. 9) and packaged *in vitro* (ref. 21). Recombinant phage were screened with the 3' *Pst*I-*Sal*I fragment of molecularly cloned *v-myc* (ref. 7) by *in situ* plaque hybridization (ref. 10). The transcriptional orientation of *c-myc* was determined by using as probes the 5' and 3' *Pst*I-*Sal*I fragments of molecularly cloned *v-myc* (ref. 7). The presence and organization of FeLV sequences were determined by using as probes a molecularly cloned FeLV LTR, the U3 region of the FeLV LTR, and a complete FeLV provirus (ref. 8). Illustrated are the feline DNA insertions bounded by *Eco*RI recognition sites contained in the bacteriophage vector⁹. Each region demarcated by a box represents a FeLV LTR. Arrows indicate the 5' to 3' direction of transcription. B, *Bam*HI; E, *Eco*RI; H, *Hind*III; K, *Kpn*I; SI, *Sac*I; Sal, *Sal*I.

strates that they too have integrated in two distinct locations in host DNA. Recombinants λ 103 and λ 115 have a recognition site for *Sac*I located 1 kb downstream from the *Kpn*I site in the 3' LTR (Fig. 2b), and thus λ 103 may represent a downstream continuation of λ 115. These data suggest that at least one replication or infectious event occurred after generation or acquisition of the defective provirus.

The 8-kb *Bam*HI fragment containing a full length *myc-FeLV* provirus was subcloned from λ 115 (Fig. 2b) into the plasmid pBR325 (ref. 11). A restriction enzyme site map of this fragment localizes the *myc* homology to a 1.1-kb *Pst*I-*Eco*RI fragment positioned 2 kb from the *Kpn*I site in the 5' LTR (Fig. 3). The transcriptional orientation of *myc*, determined using probes for 5' and 3' *v-myc* individually, is the same as that of the provirus. The 0.5-kb intron in feline *c-myc*, defined by the presence of the restriction sites *Bam*HI, *Sac*I and *Kpn*I (Fig. 2a), does not appear in the *myc-FeLV* provirus.

The structure of the remaining FeLV DNA resembles that of the Gardner-Arnstein (G-A) strain¹², particularly because the enzymes *Kpn*I and *Sma*I separate the U3 and U5 regions of the LTR in *myc-FeLV* (Fig. 3) and in G-A FeLV (ref. 13). Further, the recognition sites for *Sac*I, *Bgl*II, *Sma*I and *Bgl*III in the 5' region of the *myc-FeLV* proviruses are exactly as reported from restriction enzyme analysis of G-A FeLV (ref. 13), and the *Sac*II site in the envelope region was identified by nucleotide sequencing of G-A FeLV (ref. 14). However, the LTR of the *myc-FeLV* provirus contains a recognition site for *Sal*I in the U3 region (Fig. 3) which does not appear in any

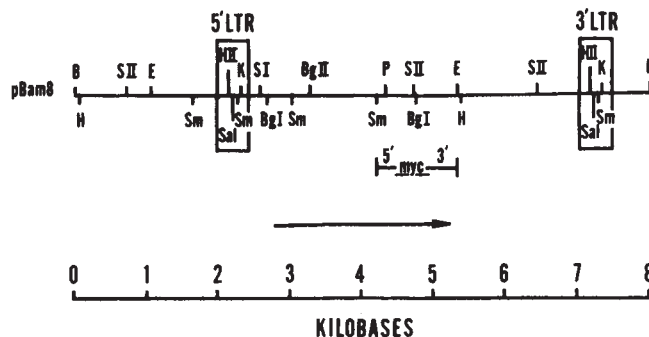


Fig. 3 Structure of the 8-kb *Bam*HI fragment isolated from the recombinant phage clone, 115 (Fig. 2b). DNA from 115 was digested with *Bam*HI and ligated into *Bam*HI-digested pBR325 (ref. 11). A recombinant plasmid containing the 8-kb fragment was designated pBam8. The arrangement of *myc* sequences was determined by using as probes the 5' and 3' *Pst*I-*Sal*I fragments of molecularly cloned *v-myc* (ref. 7). The organization of FeLV sequences was determined by using as probes a molecularly cloned FeLV LTR, the U3 region of the FeLV LTR, and a complete FeLV provirus (ref. 8). Each region demarcated by a box represents a FeLV LTR. The arrow indicates the 5' to 3' direction of transcription for the *myc-FeLV* provirus, B, *Bam*HI; BglI, *Bgl*I; BglII, *Bgl*II; E, *Eco*RI; HII, *Hind*II; H, *Hind*III; K, *Kpn*I; P, *Pst*I; SI, *Sac*I; SII, *Sac*II; Sal, *Sal*I; Sm, *Sma*I.

known isolate of FeLV (ref. 15). The LTR of *myc-FeLV* also contains a recognition site for *Hind*II in the U3 region (Fig. 3), a site whose presence distinguishes horizontally acquired from endogenous FeLV (ref. 15).

The identification of the *myc-FeLV* provirus in a thymic lymphoma (tumour 1110) is significant because it indicates that a retrovirally transduced *myc* sequence is involved in the induction of a feline tumour, a possibility not previously considered. The presence of *myc-FeLV* in lymphoid tumours is a rare event, observed in 1 of 31 tumours examined; however, the frequency may not be unexpected in light of the heterogeneity of the tumours examined. In fact, only four of the tumours represent thymic lymphomas. Two other FeLV *myc*-containing viruses have been identified independently (J. Neil and J. Mullins, personal communications).

FeLV is unusually promiscuous in its interactions with oncogenes, previously reported to have transduced the sequences *fes* (ref. 16), *fms* (ref. 17), *fgr* (ref. 18), *sis* (ref. 19) and *abl* (ref. 20) in isolates from naturally occurring tumours. The isolation of a *myc-FeLV* provirus reported here is unique among these in two respects. First, the *myc-FeLV* provirus was identified from a tumour of haematopoietic origin, while the other defective feline strains, collectively referred to as feline sarcoma viruses (FeSV), were isolated from fibrosarcomas¹⁶⁻²⁰. More importantly, whereas the FeSV isolates were identified by virtue of their focus-forming activity in an *in vitro* transformation assay¹⁶⁻²⁰, the *myc-FeLV* provirus was identified because it appeared as a structural anomaly during a broad survey of *c-myc* organization in naturally occurring feline lymphomas. In fact, the molecularly cloned *myc-FeLV* provirus (pBam8; Fig. 3) does not have the capacity to transform NIH 3T3 cells in culture (S. Caradonna, personal communication).

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Viral transduction of *c-myc* gene in naturally occurring feline leukaemias

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Feline leukaemia virus (FeLV) is epidemiologically associated with induction of the majority of lymphoid tumours of the domestic cat¹. However, about one-third of these tumours are devoid of exogenous virus or show evidence of virus integration only after tumour outgrowth^{1,2}. To help define the genetic mechanisms of feline lymphomagenesis we have explored here the possibility that cellular oncogenes (*c-onc* genes) are rearranged in tumour cell DNA. Of 16 FeLV-positive T-cell tumours among 31 naturally occurring lymphomas, 2 showed evidence of recombinant FeLV proviruses containing *myc* oncogene sequences. One of the two produced a transmissible *myc*-containing FeLV. In both cases *c-myc* and its surrounding DNA appeared unaltered. We believe that the association of *myc* with FeLV may result in its activation and play a part in the development of a significant fraction of cat T-cell lymphomas. Our findings contrast with studies of experimental induction of chicken lymphoma, in which *myc* activation occurs by retrovirus promoter insertion near *c-myc* (refs 3-5), rather than by incorporation into virus.

Twenty-one tumours (16 T-cell, 1 B-cell, 4 mixed cell or unclassified) were found to be virus positive and 10 (3 T-cell, 4 B-cell, 3 mixed cell or unclassified) as virus negative by hybridization with an exogenous FeLV specific probe (exU3)^{2,6}. Tumour DNAs were probed with up to 11 viral oncogenes, namely *myc*, *src*, *erb*, *myb*, *sis*, *abl*, *mos*, *fes*, *fms*, *ras*^H and *ras*^K. Clear evidence for alterations in hybridization pattern was detected in two tumours, each involving the *myc* oncogene.

For detailed analysis of these two tumours we used probes derived from the feline *c-myc* locus after cloning this region from normal cat DNA in the new bacteriophage λ vector (J1) described in the legend to Fig. 1. The probes designated BBC and HBE (Fig. 1) were subcloned from regions corresponding to the two *v-myc* homologous regions (exons) from the *c-myc* locus. A third probe, HRD, was derived from a single-copy DNA sequence located 6 kilobases (kb) 5' to the exon sequences.

Cleavage of control cat cellular DNA with *Kpn*I and hybridization with the HRD probe results in detection of a 8.7-kb band encompassing the 5' portion of the *c-myc* locus (Fig. 1). The BBC probe spans a *Kpn*I site and detects the same 8.7-kb *Kpn*I band as well as a slightly larger, 8.8-kb band extending through the 3' portion of the locus. The HBE probe detects only the 3' band.

Cleavage of DNA from the FeLV-positive thymic leukaemia-derived cell line F422 (ref. 7) with *Kpn*I and hybridization with

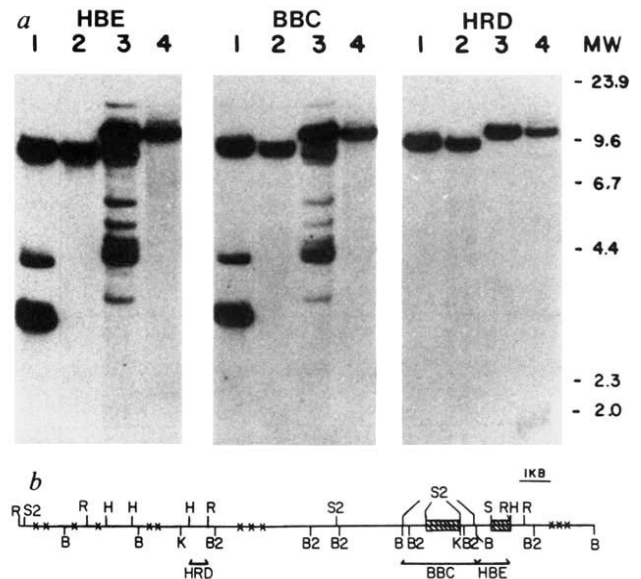


Fig. 1 *myc* sequences in the F422 cell line. **a**, Three identical nitrocellulose filters were hybridized with probes derived from the feline *c-myc* locus described below. Each panel consists of F422 passage 45 DNA (lanes 1, 3) and control DNA (derived from specific pathogen-free cat lymph node; lanes 2, 4). Before electrophoresis, DNAs in lanes 1 and 2 were digested with *Kpn*I and in lanes 3 and 4 with *Hind*III. Molecular weight (MW) marker sizes are given in kilobase pairs on the right. The lower part of the figure depicts the restriction map of the molecularly cloned feline *c-myc* locus and the origin of the probes used in the upper panels. Fragments marked with (x) symbols contains sequences highly reiterated in the cat genome. The hatched boxes correspond to regions of homology to the chicken *v-myc* gene²⁶. The orientation of DNA relative to the *v-myc* coding sequence are 5' to 3' going from left to right. The restriction site designations are abbreviated as follows: R, *Eco*RI; S2, *Sac*II; B, *Bam*HI; H, *Hind*III; K, *Kpn*I; B2, *Bgl*II; S, *Sma*I. The positions of additional *Sac*II and *Sma*I sites outside the immediate region of *v-myc* homology were not mapped.

Methods: **a**, 7.5 μ g of total cellular DNA was digested with the enzymes indicated, electrophoresed, transferred to nitrocellulose and hybridized with ³²P-nick-translated probes in the presence of 10% dextran sulphate and 50% formamide and processed as described previously²⁷. **b**, SPF cat lymph node DNA was partially digested with *Mbo*I and fragments separated according to size then ligated with vector, packaged *in vitro* and the resultant library screened with *v-myc* using protocols described previously²⁸. The vector used was λ J1, a derivative of bacteriophage λ L47.1 (ref. 29) created by substitution of 95 base pairs of the synthetic poly-linker of π VX (ref. 30) (containing the restriction sites *Eco*RI, *Cl*AI, *Hind*III, *Xba*I, *Bgl*II, *Pst*I and *Bam*HI) for the 2.0- and 2.3 kb *Eco*RI-*Bam*HI fragments of λ L47.1. λ J1 is used for cloning *Mbo*I, *Bam*HI, *Eco*RI, *Hind*III, *Xba*I, *Bgl*II and *Bcl*I fragments 8-24 kb in length and *Xho*I and *Sal*I fragments 2-18 kb in length. Two overlapping molecular clones (λ SPF 61 and 62) were mapped for: restriction sites²⁷, positions of highly reiterated sequences using normal cat DNA as probe²⁸, and *v-myc* homology. The fragments indicated below the composite map were subcloned into the plasmid pUC8 (ref. 31) after digestion with *Hind*III and *Eco*RI, (pSPF61-HRD); *Bam*HI (pSPF62-BBC); or *Hind*III and *Bam*HI (pSPF 63-HBE). Plasmid inserts were gel purified³² before use as probe.

either BBC or HBE probes results in detection of a major new 3.2-kb band and a minor new 4.1-kb band in addition to the expected pattern. This suggests that the *Kpn*I site between the two exons was lost and that new *Kpn*I sites are introduced, closely flanking the exons. When the HRD probe is used, no evidence of *c-myc* rearrangement is detected. Thus the new *myc* exon sequences appear to reside at chromosomal loci distinct from that of *c-myc*.

*Hind*III digestion of control cat DNA results in a 10.3-kb fragment which encompasses all three probe fragments (Fig. 1). This band is detected by each probe in F422 DNA; however, the BBC and HBE exon probes also detect several new bands.

Fig. 2 Genomic DNA analysis of F422 virus-infected and uninfected mink lung cell line DNA. Lane 1 is uninfected mink lung cell DNA, digested with *Kpn*I and probed with BBC. Lanes 2 and 3 are F422 virus infected mink lung cell DNA digested with *Kpn*I and probed with BBC (lane 2) or exU3 (lane 3). Molecular weight markers are as in Fig. 1.

Methods: The F422 virus infected cell line was created by feeding a freshly plated subconfluent monolayer of mink lung fibroblasts with 6-h old F422 (high passage) cell supernatant which had been passed through a 0.22- μ m filter. Thereafter, cells were fed twice a week with fresh media and passaged once a week. Production of extracellular reverse transcriptase was detected after 4 weeks²⁷ and DNA extracted and analysed. The autoradiograms shown in lanes 2 and 3 are from a single nitrocellulose filter initially hybridized with the BBC probe. Bound probe was then removed by incubation of the filter at 70 °C for 30 min in 50% formamide, 0.015 M sodium chloride, 0.0015 M sodium citrate, 0.1% sodium lauryl sarkosine and 0.05% sodium pyrophosphate. The filter was then prehybridized and hybridized with the exU3 probe as described in Fig. 1 legend.

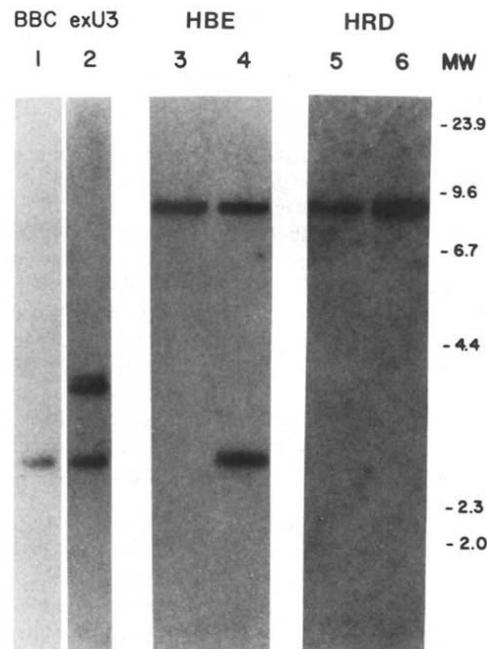
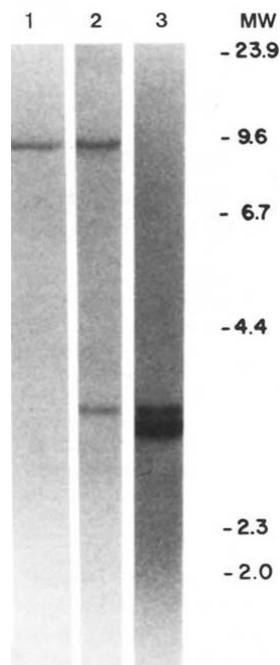


Fig. 3 Analysis of pet cat 80-15467 tumour DNA. Each sample was digested with *Kpn*I before electrophoresis. Lanes 1,2,4 and 6 contain chest tumour DNA from pet cat 80-15467. Lanes 3 and 5 contain control DNA as described in the legend to Fig. 1. The autoradiograms shown in lanes 1 and 2 are from a single nitrocellulose filter hybridized with BBC, the probe removed as described in the legend to Fig. 2 and then hybridized with exU3. Lanes 3 and 4 and lanes 5 and 6 were hybridized with the HBE and HRD probes respectively.

The HRD probe again fails to detect any rearrangement of the *c-myc* locus, thus supporting our previous conclusion that the additional *myc* exon sequences reside at new locations.

The new *Hind*III fragments detected with HBE and BBC probes appear to be of less than single-copy intensity (Fig. 1), suggesting that different *myc* exon arrangements occur within subpopulations that were present in the cell line at early passage (passage 45). Examination of F422 cells at later passages confirms the heterogeneity of position of the new exon bands with one or two patterns predominating at high passage (data not shown).

We considered the possibility that the new *myc* sequences occur as a result of transduction by FeLV. However, it was not possible to determine accurately whether the new *myc* sequences were found adjacent to FeLV sequences, since this cell line contains more than 50 exogenous FeLV proviruses per cell, thus obscuring whether *myc* and FeLV bands co-migrate (data not shown). To test the hypothesis that the new *myc* sequences were incorporated within a transmissible FeLV provirus, we exposed mink lung cells to a cell-free supernatant from F422 cells and monitored the cells 4 weeks later for the presence of exogenous FeLV and *myc* cross-reactive sequences (Fig. 2). As predicted by the transduction hypothesis, new *myc* cross-reactive bands were detected, each of which hybridized to the exogenous FeLV specific probe exU3 (ref. 6). Nearly all oncogene-containing retroviruses capture cellular genetic information at the expense of viral genes required for replication and as a result are horizontally transmitted only in the presence of an excess of replication competent helper virus⁸. The relative intensity of exU3-homologous bands in mink lung cells indicates that the *myc*-containing recombinant virus from F422 cells corresponds to a minor population of FeLV proviruses, as expected for a replication-defective virus.

Alteration to *myc* was also detected in a tumour mass taken directly from a pet cat with a thymic lymphoma (Fig. 3). As in the case of the F422 recombinant virus, the novel *myc* sequences appeared to be incorporated into an FeLV provirus, since *Kpn*I digestion to tumour DNA resulted in a new, 2.5-kb band which hybridized with both HBE and BBC probes; and once again the HRD probe failed to detect rearrangement at the *c-myc* locus.

The viral exU3 probe hybridizes specifically to horizontally transmissible FeLV long terminal repeat (LTR) sequences 5' to the *Kpn*I site found in each LTR (refs 2, 6). Therefore the finding that this probe also hybridizes to the novel *myc* band in the pet cat tumour demonstrates that *myc* sequences are found adjacent and 5' to a viral LTR, as expected for a recombinant virus with an oncogene inserted near the 3' end.

Activation of *c-myc* oncogene sequences has been detected in retrovirus-induced B-cell lymphomas of chickens³⁻⁵, and in a minority of rat thymomas induced by murine leukaemia virus⁹. *c-myc* alterations have also been detected in tumours without known retrovirus involvement, including mouse T-cell tumours¹⁰, mouse plasmacytomas^{11,12} and Burkitt lymphomas of humans¹². Avian retroviruses which have transduced the *myc* gene are capable of efficiently inducing myelocytomatosis¹³, T-cell lymphomas¹⁴, and sarcomas and carcinomas in chickens, and of transforming fibroblasts, myeloid cells and epithelial cells in tissue culture¹³. Our findings and similar findings reported by Neil *et al.*¹⁵ and Levy *et al.*¹⁶ in the accompanying papers extend the known involvement of *myc* in oncogenesis to a significant fraction of naturally occurring T-cell lymphomas of cats. *In vitro* transfection studies suggest that under certain circumstances an activated *myc* gene leads to immortalization of cells in the multistep process of tumorigenic cell transformation of primary rat fibroblasts (ref. 17; H. Land, personal communication). We do not yet know whether these FeLV-*myc* recombinant viruses are acutely oncogenic and capable of inducing short-latency tumours in inoculated animals as are their avian virus counterparts.

Natural and experimental lymphomas seem most often to arise by different mechanisms. The natural cat lymphomas, studied by us and by Neil *et al.*¹⁵ and Levy *et al.*¹⁶, included seven examples where the *myc* gene was found incorporated into the FeLV genome, and only one example where *c-myc* had undergone some form of chromosomal rearrangement. By contrast, about 90% of experimental bursal lymphomas induced in chickens by avian leukaemia virus^{4,5,18} and two out of four

mental cat lymphomas induced by FeLV showed virus promoter insertion near *c-myc*¹⁵, and incorporation of *myc* into the viral genome did not occur. We suspect that this difference arises for the following reason. To produce lymphomas quickly, young animals are inoculated with a large dose of a highly leukaemogenic strain of virus¹⁹⁻²¹; it is likely that many potential target cells are infected with virus, and activation of *c-myc* via promoter insertion occurs in a sufficient number of cells that at least one cell undergoes the additional necessary genetic alterations required for tumour formation²² (such as activation of a gene analogous to the B-*lym* gene found in chicken bursal lymphomas²³). In natural conditions of virus exposure, the incidence of viraemia is lower and tumour latency is longer in viraemic animals, thus far fewer target cells are likely to be infected, and then usually with virus of low leukaemic potential. Although a slower and rarer event than promoter insertion, transduction of oncogenes into appropriate target cells may be the more usual and efficient way of forming a tumour in a natural setting.

There are other tumours in which tumour-specific virus integration sites have not been detected, including bovine B-cell leukaemia²⁴ and human adult T-cell leukaemia²⁵. It will be interesting to see whether oncogene transduction is involved in the development of these tumours and whether transduction of genes other than *myc* might account for induction of the remainder of the cat lymphomas we have studied.

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Inversion of chromosome 14 marks human T-cell chronic lymphocytic leukaemia

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Rare cases of chronic lymphocytic leukaemia (CLL) in man stem from the malignant proliferation of T cells. The disease is usually more aggressive clinically than B-cell-derived CLL. Various haematological tumours are associated with specific chromosome aberrations (for example, refs 1, 2). Only limited numbers of T-cell CLL patients have so far been studied cytogenetically and, whereas chromosome 12 seems particularly to be involved in B-cell CLL³, several markers have been found in T-cell tumours^{4,6-9}. Recently, by stimulating malignant clones with different mitogens, novel chromosome abnormalities have been detected in T-cell CLL⁵. Using the same approach for additional cases of T-cell CLL, we now report that the most consistent chromosome change is an inversion of the long arm of chromosome 14, *inv*(14)(q11 q32), in four of five patients. Another remarkable chromosome aberration is trisomy for the long arm of chromosome 8, found in three of five patients.

Five patients with T-cell CLL were investigated. At the time of sampling, no therapy had been initiated in four of the patients. Chromosome analysis (Table 1) was performed on peripheral blood lymphocytes after stimulation with a variety of T-cell activators. As the malignant T cells are of clonal origin, only a few of the mitogens used produced proliferative responses, a finding noted previously^{4,5}. The results of the chromosome analysis after stimulation with phytohaemagglutinin (PHA) are shown in Table 1.

Several chromosome markers were observed in the five patients but we believe that the *inv*(14)(q11 q32) marker (Figs 1, 3a) seen in four of the five patients is the most significant. This marker has previously only been observed in the lymphosarcoma line, U-698 (ref. 2). Recent data suggest that the marker may be present in normal cell cultures (B. Dutrillaux, personal communication). However, we re-examined karyotypes of more than 100 tumours, cell lines established from tumours and several hundred normal subjects, and found no additional case showing the *inv*(14) marker.

Aberrations of chromosome 14 have been observed in a number of different haematological tumours¹⁰; the most notable is perhaps the translocation (t(8; 14) in Burkitt's lymphoma², in which the breakpoint on chromosome 14 is normally located in q32, the region encoding the immunoglobulin heavy-chain genes¹¹, but in exceptional cases is observed in q11 or q13 (refs 8, 12). Both these sites contribute to the formation of the *inv*(14) marker seen in our patients. In studies on the virally induced adult T-cell leukaemia in Japan, a 14q+ marker, with attachment of different autosomes to q32, has frequently been observed^{7,9}, suggesting that genes in this region may contribute to the pathogenesis of T-cell tumours.

The *inv*(14) marker could not be demonstrated in a total of 277 metaphases of one of the patients (patient 5) despite repeated attempts using several different mitogens. The lack of this putatively specific T-cell CLL marker could be related to

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Table 1 Chromosome markers in patients with T-cell chronic lymphocytic leukaemia after stimulation with PHA

Patient (ref. 5)	No of metaphases studied*	No. of metaphases with markers	Markers
1	18	17	inv(14): 17/17, t(8p-; 8q) 8/17, der(18) (18qter→ p13::11p14→11pter):17/17, t(21q; 22q-):17/17
2	12	7	inv(14):6/7, t(8q; 8q)6/7, 5p+:5/7, 7q+:4/7, 9q+:5/7, t(9q; ?):4/7
3	7	4	inv(14):3/4, t(4; 12) (4 pter→ qter:: 12q13→ qter):3/4, 3p-:3/7m 6p+:3/4, 7p+:4/7, 11p-: 3/4, 12 q-: 6/4, t(19; ?): 4/4
4	31	31	t[inv(14); 22]:29/31, t(8p-; 8q):16/31, t(6; 12q):30/31, t(17q; ?):29/31
5	42	19	4q-:2/19, 6q-:17/19

* Total number of metaphases studied after stimulation with phytohaemagglutinin or other mitogens (in parentheses per cent abnormal metaphases): patient 1, 77 (69%); patient 2, 98 (59%); patient 3, 36 (33%); patient 4, 77 (79%); patient 5, 103 (57%). Chromosome preparations were made according to conventional methods. After isolation metaphases were stained by Q (ref. 20) and G (ref. 21) banding, in some cases also by R (ref. 22) and C (ref. 23) banding. The modal chromosome number was 46,XX (patients 1, 4 and 5) and 46,XY (patients 2 and 3).

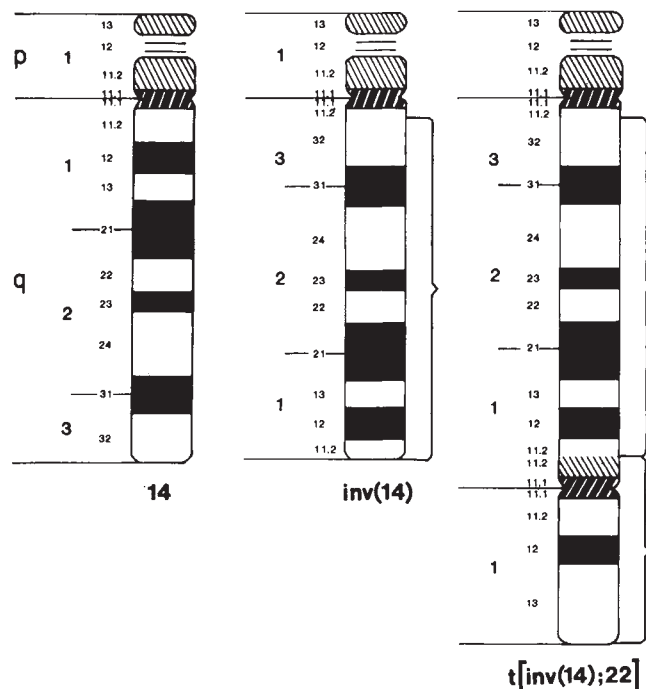


Fig. 1 Arrangement of bands in a normal chromosome 14, the inverted chromosome 14 in patients 1, 2 and 3 and a translocation between an inv(14) and a chromosome 22 in patient 4.

the relatively benign form of disease in this patient (who still receives no treatment) and may suggest that inv(14) is a marker for malignant disease. Eventually, this marker may develop during the natural history of the T-cell CLL, thus transforming the disease into a clinically more aggressive form.

Another marker that deserves attention is the translocation between two chromosomes 8, found in three patients (1, 2 and 4). Clones with this marker (Figs 2, 3b) possess only one normal chromosome 8 and are trisomic for 8q and monosomic for either the whole (patient 2) or the distal part of the short arm (patients 1 and 4). In these cases, the important aberration seems to be the trisomy of the long arm but not the localization of the breakpoint in the short arm (8p) or the centromere (8c) since that varies in the three patients. Two important oncogenes are located on 8q, *c-mos* and *c-myc*¹³. The three cases with trisomy for 8q are thus in agreement with the gene-dose effect hypothesis of tumorigenesis suggested by Klein¹⁴.

In one of the patients (patient 4), chromosome 6q-, a marker frequently found in several haematological disorders¹⁰, including adult T-cell leukaemia^{6,9}, carries the distal segment of chromosome 12 (q21→qter). In another patient (patient 3), the segment 12q13→qter is attached to chromosome 4. In both patients who possess only one normal chromosome 12, the breakpoint is localized close to 12q13-15, the region of the chromosome considered important for the development of B-cell CLL¹⁵ and also for benign salivary gland tumours¹⁶ and

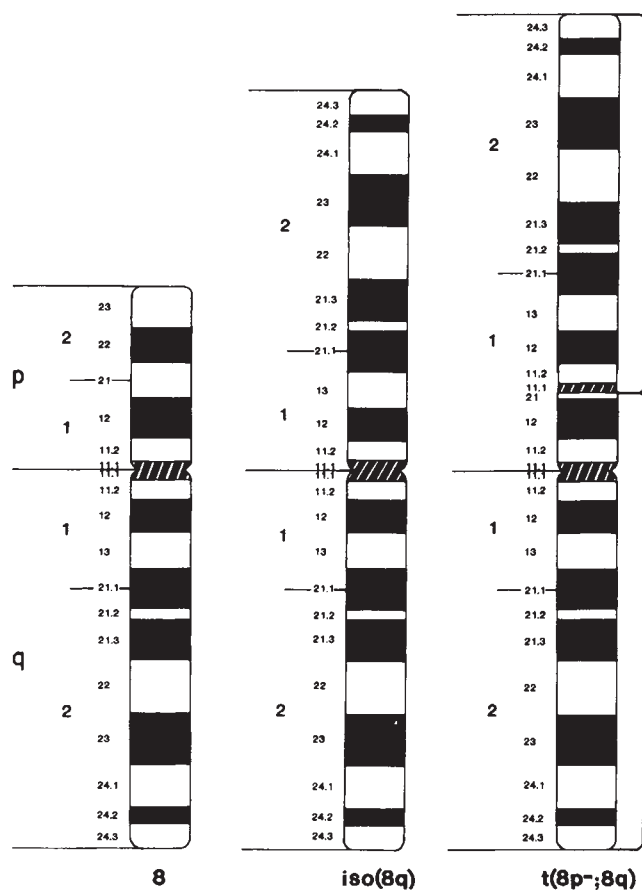


Fig. 2 Arrangement of bands in a normal chromosome 8, the iso(8q) in patient 2 and the t(8p-; 8q) in patients 1 and 4.

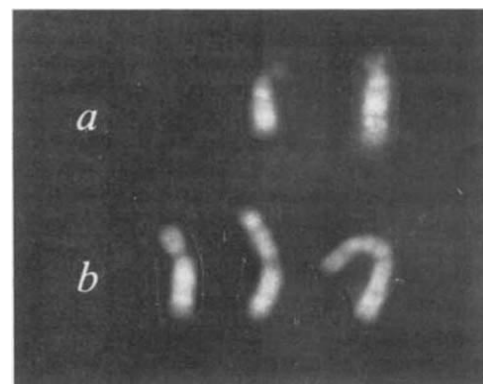


Fig. 3 a, From left to right: a normal chromosome 14, inv(14) and t[inv(14); 22]. Q-banding, $\times 2,500$. b, From left to right: photograph of a normal chromosome 8, iso(8q) and t(8p-; 8q). Q-banding, $\times 2,500$.

adenoid cystic carcinoma¹⁷. Although there is as yet limited information on the localization of oncogenes, these findings are of interest with regard to the observation that an oncogene of the *c-ras* family seems to be located on 12q24 (ref. 18).

The high frequency of markers found in untreated T-cell CLL patients suggests that tumour development is a multistage process in which the acquirement of the *inv(14)* marker is a crucial step. Furthermore, in the mouse, a cluster of tightly linked genes, distal to the immunoglobulin heavy-chain locus, encode cell-surface products regulating T-cell maturation and T-cell immunocompetence¹⁹. It is attractive, therefore, to speculate that similar genes are present on chromosome 14q32 in man and may, when rearranged as in *inv(14)*, be involved in the transformation of T cells.

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Double-stranded cleavage by cell extracts near recombinational signal sequences of immunoglobulin genes

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The genes encoding the variable regions of murine immunoglobulin light chains are present in the germ line in two separate segments, *V* and *J*. During B lymphocyte differentiation these segments are brought together to form a single unit (for review see ref. 1). Although much is known about the structures of *V* and *J* segments, both in germ-line configuration and after rearrangement^{2–5}, essentially nothing is known about the biochemical mechanism of *V–J* recombination. One possible step in proposed mechanisms of immunoglobulin gene rearrangement is endonucleolytic cleavage of the participating DNA segments before joining⁶. In an attempt to detect such an activity, we have developed an assay for the detection of site-specific double- or single-strand endonucleolytic activity in crude soluble extracts. Using this assay we have detected an activity in extracts of nuclei from mouse B-lymphoid lines and from mouse L cells that is capable of introducing duplex breaks near the recombinational signal sequences of immunoglobulin *J_κ* segments. We report the activity here because of its intrinsic interest although we lack any direct evidence that it has a role in *V–J* recombination.

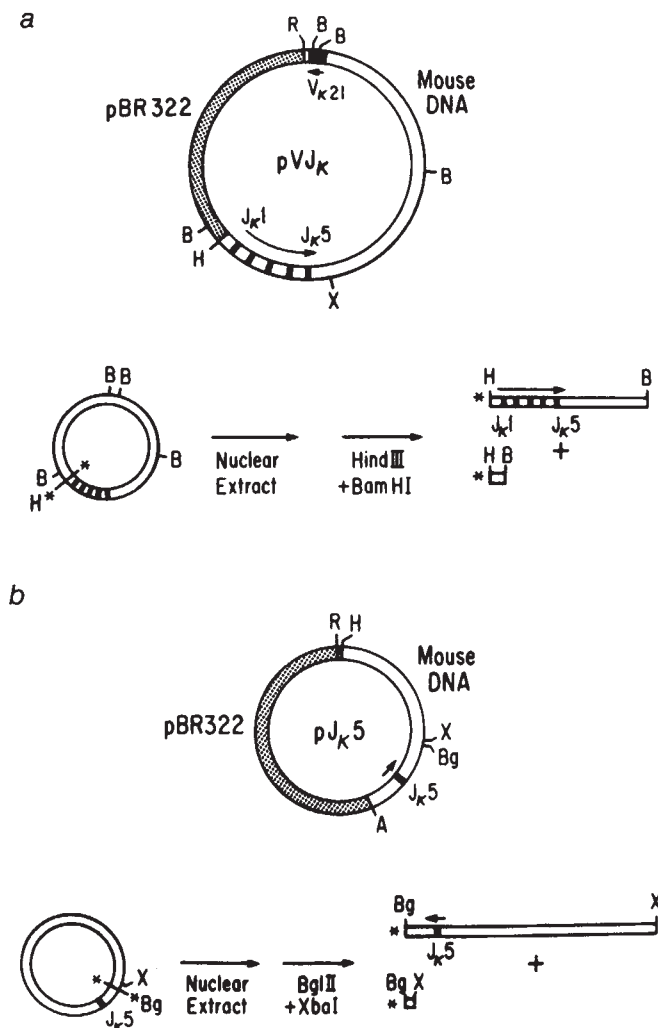
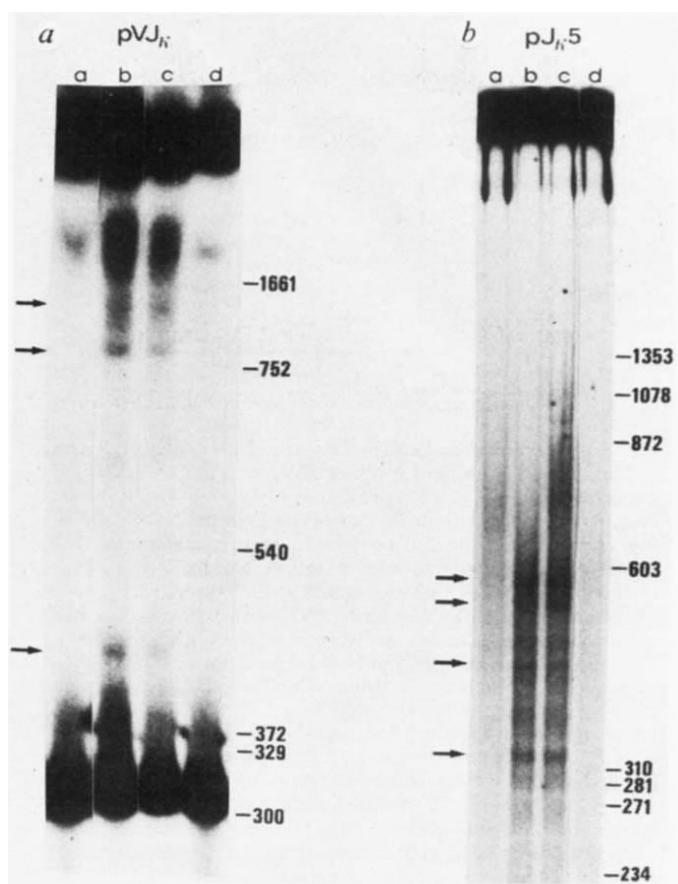


Fig. 1 Structures of DNA substrates and diagrams of endonuclease assays. **a Top:** Partial restriction map of *pVJ_κ*. The 7.4-kb fragment from the *EcoRI* site to the *XbaI* site was derived from the genomic clone *Igκ5E* (a gift of Dr Susumu Tonegawa) and contains the germ-line *V_κ* segment which is functionally rearranged in the MOPC 321 mouse plasmacytoma^{3,7}. The 1.7-kb *XbaI–HindIII* fragment was derived from a longer 2.7-kb *HindIII* fragment represented in the genomic subclone *pHJ_κ* (ref. 10) (a gift of Ms Susanna Lewis) and contains the five BALB/c *J_κ* segments in their germ-line configuration. The third part of the construction consisted of the 4.3-kb *EcoRI–HindIII* fragment of *pBR322*. The small arrows at the sites of the *V_κ* and *J_κ* segments indicate the transcriptional orientations of these sequences. **Bottom:** Use of *pVJ_κ* in the site-specific endonuclease assay. To prepare the substrate for the assay, the plasmid was linearized with the *HindIII* restriction enzyme, which cleaves 81 bp to the 5' side of the *J_κ1* coding sequence. The ends of the molecule were dephosphorylated with calf intestinal phosphatase and radiolabelled by phosphorylation with [γ -³²P]ATP and polynucleotide kinase. Following phosphorylation, the plasmid was recircularized by *T₄* ligase in conditions that yielded predominantly monomeric circles. Recircularization served to protect the substrate from dephosphorylation and exonucleolytic degradation in the crude extract. **b Top:** Partial restriction map of *pJ_κ5*. This construction was made by digestion of *pHJ_κ* with *AccI*, followed by blunting of recessed 3' ends with the Klenow fragment of DNA polymerase I and ligation with *T₄* DNA ligase. The resulting plasmid contained 2,274 bp of *pBR322* (including the origin of replication and the ampicillin resistance gene) and 1,626 bp of BALB/c DNA extending from the *AccI* site within the *J_κ4–J_κ5* spacer region to the *HindIII* site about 1.3 kb to the 3' side of *J_κ5*. **Bottom:** Use of *pJ_κ5* in the site-specific endonuclease assay. To prepare the substrate for the assay, the plasmid was linearized with the *BglII* restriction enzyme, which cleaves 257 bp to the 3' side of the *J_κ5* coding sequence. The molecule was dephosphorylated, radiolabelled and recircularized as described above.

Fig. 2 Assay for endonuclease activity with pVJ $_{\kappa}$ or pJ $_{\kappa}$ 5. **a**, Assay with pVJ $_{\kappa}$ substrate. Lane a, no incubation. Lane b, incubation for 30 min in standard conditions. Lane c, incubation for 30 min without addition of ATP. Lane d, incubation for 30 min without addition of MgCl $_2$, in the presence of 20 mM EDTA. Incubation of reaction mixtures for 60 and 120 min resulted in progressively greater overall degradation of the substrate without significant enhancement of specific bands (data not shown). The positions and sizes (in bp) of DNA length standards are indicated. **b**, Assay with pJ $_{\kappa}$ 5 substrate. Lane a, no incubation. Lane b, incubation for 30 min in the presence of 500 ng pV $_{\kappa}$ 15 (a plasmid containing the V $_{\kappa}$ 21-C gene in its germ-line configuration). Lane c, incubation for 30 min without pV $_{\kappa}$ 15. Lane d, incubation for 30 min without nuclear extract. The positions and sizes (in bp) of DNA length standards are indicated.

Methods: **a**, Cells of the PD31 lineage¹⁰ were cultured in RPMI 1640 supplemented with 10% fetal calf serum and 50 μ M β -mercaptoethanol. For this experiment, cells were grown in the presence of 10 mM 3-aminobenzamide (an inhibitor of ADP-ribosyltransferase activity)¹⁶ for 24 h before collection; in all subsequent experiments treatment with 3-aminobenzamide was omitted, with no difference in activity of extracts. One litre of cells, grown to a density of 2×10^6 cells per ml, was collected by centrifugation at 1,000g for 5 min at 4°C. Cells were washed in 20 ml of a buffer containing 20 mM HEPES pH 7.5, 5 mM KCl, 0.5 mM MgCl $_2$, 0.5 mM dithiothreitol (DTT) and 0.2 M sucrose and collected by centrifugation at 1,000g for 5 min at 4°C. Cells were resuspended in 5 ml of a buffer containing 20 mM HEPES pH 7.5, 5 mM MgCl $_2$, 5 mM KCl, 0.5 mM DTT and allowed to remain on ice for 10 min. Cells were disrupted by homogenization and 5 ml of a buffer containing 20 mM HEPES pH 7.5, 5 mM MgCl $_2$, 5 mM KCl, 0.5 mM DTT and 0.4 M sucrose were added to the lysate. Nuclei were collected by centrifugation at 120g for 5 min at 4°C. The nuclear pellet was resuspended in 2.5 ml of a buffer containing 50 mM HEPES pH 7.5 and 10% sucrose. Nuclear extracts were prepared by adding NaCl to 100 mM final concentration followed by incubation for 1 h on ice and centrifugation at 15,000g for 20 min at 4°C. The supernatant was stored on ice. Assays were carried out at 30°C in a 50- μ l reaction mixture containing 10 mM HEPES pH 7.5, 6 mM MgCl $_2$, 2 mM ATP, 1 mM DTT, 0.1 mM EDTA, 10 ng 32 P-labelled plasmid DNA and 12.5 μ l nuclear extract. Reactions were stopped by addition of 50 μ l of a solution containing 50 mM EDTA, 1.2% SDS and 0.2 mg ml $^{-1}$ yeast tRNA. Proteinase K was added to 100 μ g ml $^{-1}$. Following incubation for 90 min at 37°C the 32 P-labelled plasmid DNA was recovered by phenol extraction and cleaved with *Hind*III and *Bam*HI. The products were separated by electrophoresis through a 5% polyacrylamide gel and detected by autoradiography. **b**, Cells were grown as described above except that 3-aminobenzamide was not added to the growth medium. Nuclei and nuclear extracts were prepared as described above. Reactions were carried out in the absence of exogenous ATP and in the presence of 500 ng salmon sperm DNA; otherwise, conditions were identical to those indicated above. The plasmid DNA was recovered as described above and cleaved with *Bgl*II plus *Xba*I (*Xba*I cleaves the plasmid at a site 31 bp from the *Bgl*II site and on the opposite side of the site from the J $_{\kappa}$ 5 segment; see Fig. 1). The products were separated by electrophoresis through a 5% polyacrylamide gel and detected by autoradiography.



sequences of J $_{\kappa}$ 2, 3, 4 or 5 would be expected to produce novel fragments of close to 434, 741, 1,064 and 1,403 bp in length^{4,8}. Cleavage near the signal sequence of J $_{\kappa}$ 1 is not unambiguously detectable in this assay because it would produce a novel fragment less than 346 bp long.

When the 32 P-labelled substrate was exposed to the nuclear extract, evidence of cleavage near the J $_{\kappa}$ segments was obtained. At zero time, digestion of the recovered pVJ $_{\kappa}$ DNA with *Hind*III and *Bam*HI yielded the expected 346-bp fragment (Fig. 2a, lane a); the 3,600-bp fragment barely entered the gel and was visible on shorter exposures as a band near the top of the lane. When the reaction was allowed to proceed for 30 min at 30°C, several additional bands were seen (lane b). Of these, the most prominent were approximately 430, 1,000 and 1,400 bp long, as expected for cleavage of the substrate near J $_{\kappa}$ 2, J $_{\kappa}$ 4 and J $_{\kappa}$ 5. No band was seen in the vicinity of 741 bp, the distance of the J $_{\kappa}$ 3 coding sequence from the labelled *Hind*III site. The absence of cleavage near J $_{\kappa}$ 3 is significant because J $_{\kappa}$ 3 appears from its sequence to be unable to function *in vivo*⁸. The activity was not dependent on the addition of exogenous ATP to the crude extract (lane c). Cleavage of the substrate near J $_{\kappa}$ 2, J $_{\kappa}$ 4 and J $_{\kappa}$ 5 was abolished by the addition of EDTA to 20 mM (Fig. 2a, lane d). The activity was not limited to extracts of nuclei from B-lymphoid cells; similar results were obtained in extracts prepared from mouse L cells (data not shown).

To simplify the endonuclease assay, we constructed plasmid

The substrate used in our initial experiments was designated pVJ $_{\kappa}$ and contained the entire germ-line cluster of five J segments of the κ light-chain family as well as a germ-line V $_{\kappa}$ segment (V $_{\kappa}$ 21-C) known to be used in the functional κ light chain of the mouse plasmacytoma MOPC 321 (refs 3, 7). Conserved heptamer and nonamer nucleotide sequences, thought to be recognition signals^{4,5,8}, were present in the substrate in association with each J $_{\kappa}$ segment and the V $_{\kappa}$ 21-C segment. The structure of pVJ $_{\kappa}$ and the assay for site-specific endonuclease activity are outlined in Fig. 1a.

Extract was prepared from the nuclei of PD31 cells, a line produced by transformation of murine adult bone marrow cells with Abelson murine leukaemia virus⁹. This line has been shown to undergo continuous, spontaneous rearrangement of the κ locus in culture¹⁰. Nuclei were prepared by homogenization in hypotonic buffer and nuclear extracts were prepared essentially as described by Challberg and Kelly¹¹. To assay for endonuclease activity, plasmid pVJ $_{\kappa}$, radiolabelled and recircularized as described in Fig. 1a, was incubated at 30°C in an appropriate reaction mixture in the presence of nuclear extract from PD31 cells (see Fig. 2 legend). The 32 P-labelled plasmid DNA was then cleaved with the *Hind*III and *Bam*HI restriction enzymes, which were expected to yield two radiolabelled fragments: one, 346 base pairs (bp) long, derived from pBR322, the other, about 3,600 bp long, derived from the inserted mouse DNA and containing the entire germ-line J $_{\kappa}$ cluster (Fig. 1a). Cleavage of the pVJ $_{\kappa}$ substrate near the recombinational signal

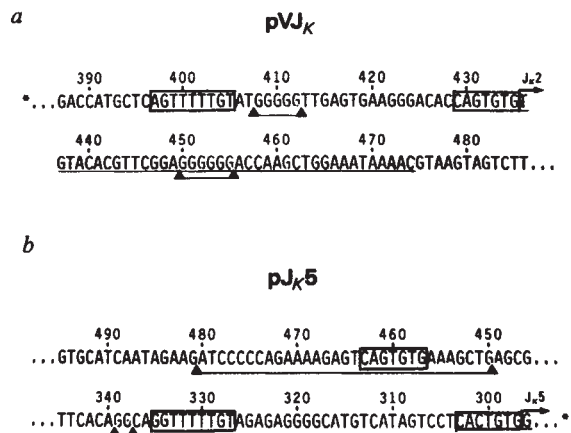


Fig. 3 Sites of endonucleolytic cleavage of pVJ κ and pJ κ 5 near J κ 2 and J κ 5. **a**, Sites of cleavage of pVJ κ near J κ 2. A portion of the germ-line J κ sequence in the vicinity of J κ 2 (refs 4, 8) is shown. Numbers indicate distance in nucleotides from the 5' 32 P-label at the HindIII site. The J κ 2 coding sequence is underlined. The conserved heptamer and nonamer sequences to the 5' side of J κ 2 are outlined by boxes. Cleavage occurs within the regions bounded by the arrowheads. The reaction of pVJ κ with extract was carried out on a preparative scale and digestion with HindIII and BamHI was performed as described in Fig. 2 legend. After fractionation of products through a 5% polyacrylamide gel, the prominent radiolabelled band of length ~450 bp was eluted. This band was the result of cleavage of pVJ κ near J κ 2. The DNA was denatured and sized on a 5% polyacrylamide-urea sequencing gel. The radiolabelled material was resolved into two bands 450–455 and 408–412 bp long. **b**, Sites of cleavage of pJ κ 5 near J κ 5. The size of the fragment produced by cleavage of pJ κ 5 near J κ 5 was determined to be 339–340 bp by polyacrylamide-urea gel electrophoresis. Two portions of the germ-line J κ sequence are shown. The first line represents part of the spacer sequence between J κ 4 and J κ 5; the second line represents part of the immediate 5' flanking sequence of J κ 5 (refs 4, 8). Numbers indicate distance in nucleotides from the 5' 32 P label at the BglII site. The start of the J κ 5 coding sequence is indicated. Conserved heptamer and nonamer sequences to the 5' side of J κ 5 and the homologous heptamer within the J κ 4–J κ 5 spacer region are indicated by boxes. Cleavage occurs within the regions bounded by the arrowheads.

pJ κ 5, containing only J κ 5 (Fig. 1b). Plasmid pJ κ 5, labelled with 32 P at its unique BglII site, was incubated with extract from PD31 nuclei and then cut with BglII plus XbaI. Without incubation, the expected large BglII–XbaI fragment was produced (a 31-bp fragment was run off the gel) (Fig. 2b, lane a). Incubation for 30 min at 30°C generated additional fragments (lane b). Identical results were obtained whether plasmid pV κ 15, containing the germ-line V κ 21-C segment, was present (Fig. 2b, lane b) or absent (lane c). The most prominent bands were about 320, 450, 530 and 560 bp long. The size of the 320-bp fragment is consistent with cleavage of the substrate near the recombinational signal sequences of J κ 5. The additional sites of cleavage are discussed below. Cleavage of pJ κ 5 was also catalysed by extracts of mouse L cells.

We have more precisely determined the sites of cleavage near J κ 2 and J κ 5 (Fig. 3). Two breaks were made in pVJ κ near J κ 2; these were located at two clusters of guanylate residues, one within the 23-bp spacer region and the other within the J κ 2 coding region. The break made in pJ κ 5 occurred 2–3 bp to the 5' side of the conserved nonamer sequence at a pair of guanylate residues. These positions do not necessarily represent the actual sites of endonucleolytic cleavage, because they could be the result of combined endonuclease and exonuclease activities.

We have thus developed an assay for site-specific endonucleolytic cleavage of DNA in crude, cell-free extracts. Using

this assay, we find an activity in nuclear extracts of B-lymphoid and fibroblast lines which results in double-strand cleavage of DNA near the putative recombinational signal sequences of J κ segments. We do not know if this activity is related to the overall process of immunoglobulin gene rearrangement and several observations lead us to interpret the results with caution. First, the activity is not specific to lymphoid cell lines. Second, the breaks do not occur at a unique position within each J κ segment; from the structures of reciprocal J κ recombination products we would expect cleavage to occur either at the junctions of conserved heptamer sequences and the J κ coding sequences or within the coding sequences^{12–14}. Third, the activity does not depend on the presence of a germ-line V κ gene in either *cis* or *trans*.

Other observations, however, indicate that cleavage in the crude extract may be potentiated by the conserved heptamer sequences. With the pVJ κ substrate we observe prominent duplex cleavage near J κ 2, J κ 4 and J κ 5 but not near J κ 3, where the heptamer signal sequence deviates from the consensus structure⁸. Also, the plasmid pJ κ 5 was cut at about 450, 530 and 560 bp from the labelled BglII site. The yield of the 530- and 560-bp bands was highly variable and we therefore have no further information about them. The 450-bp fragment, however, ends within the J κ 4–J κ 5 spacer region, where the sequence CAGTGTG occurs which is identical to the heptamer signal sequence of J κ 2. The 450-bp fragment results from cleavage of the substrate near this apparently adventitious signal sequence. There is, in fact, evidence for aberrant recombination into a site near this sequence in the myeloma MOPC 149¹⁵.

From this fact and from the structure of one reciprocal product of immunoglobulin rearrangement in the myeloma MOPC 41¹³, it appears that heptamer sequences, in the absence of an accompanying nonamer sequence, may occasionally direct rearrangement. Because the heptamer sequence at 450 bp is not accompanied by a nonamer sequence, as is characteristic of immunoglobulin signal sequences, this result would suggest that heptamer-like sequences alone potentiate cleavage of DNA in the extract. The heptamer is either palindromic or almost palindromic in its various appearances and thus recognition of a heptamer cannot supply directional information. Therefore, the nuclease could not be directed by an isolated heptamer to cut at an appropriate site. This argument suggests that the activity we are assaying may associate in lymphoid cells with a nonamer recognition element, giving it site specificity. We therefore feel that further investigation of this enzyme and its possible interactions with other proteins may shed light on at least one step in the process of immunoglobulin gene rearrangement.

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Signal sequence mutations disrupt feedback between secretion of an exported protein and its synthesis in *E. coli*

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Recent studies in a eukaryotic system indicate that a block in secretion can lead to a block in the translation of secretory proteins¹. This feedback on protein synthesis is thought to be a result of an interaction of the signal recognition particle with the signal sequences of nascent proteins. Genetic studies in the prokaryote *Escherichia coli* suggest that a complex secretion machinery²⁻⁶ and a similar feedback mechanism⁷ exist. In addition, mutations affecting two genes, *secA* and *secC*, thought to encode components of the bacterial secretion machinery, selectively interfere with the synthesis of exported proteins. This selective interference with translation may be a result of recognition by the secretion machinery of signal sequences. If so, alteration of the signal sequence of a particular protein by mutation should eliminate the block in synthesis for that protein. We show here that signal sequence mutants for an exported protein, maltose binding protein, prevent the block in synthesis of this protein in a *secA* mutant.

We have previously described the isolation of an amber (protein chain-terminating) mutant in the *secA* gene³. This amber mutation, which maps early in the gene, is lethal to the cell and can only be maintained in strains which contain an amber suppressor. To study the effects of the elimination of *secA* gene product on exported proteins, we introduced into the *secA* strain a temperature-sensitive (ts) amber suppressor. The *secA* *supFts* strain is called MM66. In MM66, the suppressor is inactivated at 42 °C, so that no further *secA* product can be made and cells eventually die.

To determine the effects of the *secA* on secretion, we have studied the maltose binding protein (MBP), a protein encoded by the *malE* gene, which is normally exported across the cytoplasmic membrane into the periplasmic space⁸. The synthesis of MBP, which is required for maltose transport into the cell, is inducible by the addition of maltose to the growth medium. We have shown previously that at 30 °C, the partial suppression of the *secA* amber mutation in MM66 results in a partial defect in secretion; both mature MBP and some precursor form of MBP, containing the signal sequence, are found on pulse labels. However, at 42 °C, synthesis of MBP is abolished; neither precursor nor mature MBP is found³. This result is not due to a general defect in protein synthesis, as most proteins appeared to be synthesized normally. The loss of *secA* product is specifically affecting the synthesis of exported proteins.

If the block in MBP synthesis we observe in MM66 at 42 °C is due to a block in translation caused by recognition of the MBP signal sequence by the secretion machinery, then signal

sequence mutants might counteract this block. We have described elsewhere the isolation and characterization of signal sequence mutants in the gene (*malE*) coding for MBP^{9,10}. These mutations each change an amino acid in the hydrophobic region of the signal sequence, causing a severe defect in secretion (Fig. 1) and the accumulation of mainly the precursor form of MBP in the cytoplasm. According to the signal recognition particle (SRP) model, these mutants would block the interaction of the MBP signal sequence with the secretion machinery.

To determine whether signal sequence mutants will counteract the block in MBP synthesis, we introduced three of these signal sequence mutations into MM66, using P1 transduction. In addition, all of these strains contained a *malT*^c mutation¹¹, which renders the synthesis of MBP and other proteins involved in maltose catabolism constitutive. The constitutive mutation was introduced to avoid possible problems in the induction of MBP synthesis in maltose medium, particularly in the signal sequence mutants. Examination of MBP synthesis in these strains at 42 °C revealed a marked difference between strains containing the wild-type *malE* gene and those containing signal sequence mutations in that gene. In the *MalE*⁺ strain, synthesis of MBP was greatly reduced, while synthesis of the cytoplasmic protein, elongation factor G (EF-G), is unaffected (Fig. 2). However, in the three signal sequence mutants analysed, the elimination of the *secA* product at 42 °C does not prevent MBP synthesis. Rather, the precursor of MBP accumulates. At 30 °C, MBP synthesis is observed in all four strains.

These results can be most simply explained if the effect of the elimination of the *secA* product on MBP synthesis is due to interference at a post-transcriptional step in gene expression. While it is clear that the signal sequence mutations are changing the sequence of the DNA of the *malE* gene and its RNA transcript, the most evident consequence of these mutations is to alter either the hydrophobic nature or possibly the structure of the signal sequence itself. One explanation for these findings is that the signal sequence mutants alter the protein in such a way as to make it more resistant to degradation. However, we consider this highly unlikely, as our pulse labels are for only 1 min and abnormal cytoplasmic proteins, in general, and internalized MBP precursor, in particular, are degraded considerably more slowly^{12,13}. Instead, we favour the hypothesis that elimination of the *secA* gene product causes a block in translation of MBP. If this explanation is correct, our results with signal sequence mutants suggest that this block involves a recognition of the signal sequence by some cellular component. This latter interpretation is, of course, consistent with the SRP model for protein secretion in eukaryotes.

These results and those found in the eukaryotic system change our concept of the role of the signal sequence and our understanding of the effects of signal sequence mutants. Earlier models of secretion assumed that the hydrophobic core of the signal sequences functioned by interacting with the membrane. It was thought that signal sequence mutations of the type described here, most of which introduce charges into this hydrophobic core, prevented secretion by interfering with hydrophobic interactions with the membrane. However, if the interpretation of the present results and those of Walter and Blobel¹ is correct, a major function of the signal sequence is its recognition in the cytoplasm by SRP or its equivalent. Nevertheless, because of the nature of the signal sequence and the classes of mutations detected, it appears that a hydrophobic interaction is important at this stage. It is not known whether the signal sequence also

met lys ile lys thr gly ala arg ile leu ala leu ser ala leu thr thr met met phe ser ala ser ala leu ala
 ↓ ↓ ↓
 pro lys arg
 10-1 16-1 18-1

Fig. 1 Amino acid changes in signal sequence mutants in maltose binding protein. The determination of the sequence changes is reported by Bedouelle *et al.*¹⁰.

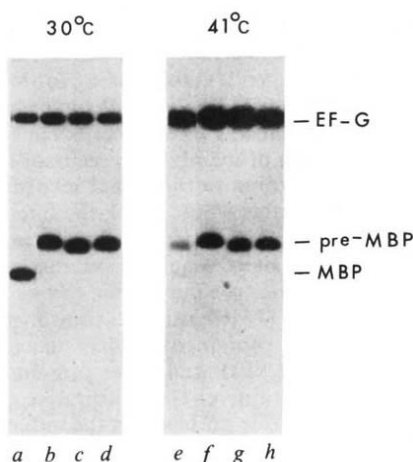


Fig. 2 Synthesis of MBP and mutant MBP. Lane a, MM113 (*malE*⁺), 30 °C; lane b, MM114 (MM113, *MalE10-1*), 30 °C; lane c, MM115 (MM113, *MalE16-1*), 30 °C; lane d, MM116 (MM113, *MalE18-1*), 30 °C; lane e, MM113, 41 °C; lane f, MM114, 41 °C; lane g, MM115, 41 °C; lane h, MM116, 41 °C.

Methods: Strain MM66 (*F*[−] *araD lacU169 rpsL relA zci::Tn10 trpam supFts secAam*) was the parent of all strains used in this experiment. A λ vir resistant, *Mal*[−] derivative of MM66 was isolated. This strain contained a *malT* mutation and was transduced to *Mal*⁺ using Plvir grown on a strain carrying a *malT*^c mutation, giving strain MM113 (MM66, *malT*^c). *MalE* signal sequence mutations were introduced into MM113 using a Tn5 insertion close to the *malE* gene (isolated by Howard Shuman) as a P1 co-transducible marker. Cells of all strains were grown at 30 °C to mid-log phase. Half of the culture was diluted and shifted to 41 °C; the remaining culture was labelled with ³⁵S-methionine. The diluted cultures were incubated at 41 °C for 2½ h, then labelled with ³⁵S-methionine. All labellings were done with 20–25 μ Ci ml^{−1} for 1 min and extracts were made by denaturing in SDS as described previously¹². Extracts were immunoprecipitated with a mixture of anti-EF-G and anti-MBP antisera and the immunoprecipitates analysed by fluorography after SDS-polyacrylamide gel electrophoresis. The detailed procedures for making of extracts and immunoprecipitation¹² and fluorography¹⁴ have been described previously.

inserts in the membrane and whether this insertion is important in secretion.

We do not know the role of the SecA protein in secretion, nor can we say how similar the secretion mechanisms are in prokaryotes and eukaryotes. However, speculation on the role of the SecA protein is simplest if we assume an SRP-like model for bacteria. Based on the properties of *secA* mutants, the SecA protein could be the part of an SRP-like complex that directly interacts with the SRP receptor in the membrane. Elimination of SecA protein would then prevent SRP from interacting with the membrane and lead to a permanent block in the translation of secretory proteins. Alternatively, SecA protein could have a structural role in a SRP-like complex. Elimination of any of several components of the complex might disrupt its structure in such a way that its ability to bind to SRP receptor is abolished, but its ability to block translation is not. Although its solubility properties make the last explanation less likely, SecA protein could itself be the SRP receptor in the membrane. Further studies on other gene products involved in secretion and analysis in an *in vitro* secretion system should distinguish between these possibilities. Finally, we point out that these experiments may concern only the earliest steps in the secretory pathway and have no relevance to the question of whether secretion is co- or post-translational.

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Stimulation of *Acanthamoeba* actomyosin ATPase activity by myosin-II polymerization

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Phosphorylation of the regulatory light chains of vertebrate smooth muscle or cytoplasmic myosins alters the structure of myosin monomers^{1–3}, favours myosin filament formation^{5,6} and stimulates the actin-activated Mg^{2+} -ATPase of myosin (for reviews see refs 7–9). Similarly, in *Dictyostelium*¹⁰ and *Acanthamoeba*^{11–13} phosphorylation of the myosin heavy chains inhibits both polymerization and actin-activated Mg^{2+} -ATPase. Unfortunately, the relationships between phosphorylation, myosin assembly and activation of ATP hydrolysis are not fully understood in any of these systems, as there has been no way of varying the extent of polymerization of intact myosin without changing solution conditions or the level of myosin phosphorylation, parameters that may have independent effects on ATPase activity. Taking an entirely new approach, we have used monoclonal antibodies against the tail of *Acanthamoeba* myosin-II that cause filament disassembly to show that myosin polymerization itself stimulates actomyosin ATPase activity. With a fixed level of myosin-II phosphorylation and constant solution conditions, depolymerization of myosin-II filaments by antibodies causes a concomitant loss of actin-activated ATPase activity.

Acanthamoeba myosin-II was purified and treated with acid phosphatase to decrease the heavy-chain phosphate level to about 0.8 phosphates per myosin molecule^{14,15}. Myosin-II forms bipolar filaments of two different sizes depending on the solution conditions¹⁵. In 0–150 mM KCl with divalent cation concentrations <5 mM, myosin-II forms thin bipolar filaments, 6 nm in diameter, consisting of 16 molecules. Thin bipolar filaments aggregate laterally in divalent cation concentrations of 5–10 mM to form thick bipolar filaments, and in these conditions the actin-activated ATPase is also stimulated¹¹.

To analyse the relationship between myosin polymerization and actin-activated ATPase activity, we selected 5 out of 23 anti-myosin antibodies that have been characterized in detail (D.P.K., T.D.P., and D. A. Kaiser, manuscripts in preparation). Antibody binding sites on myosin-II were determined by antibody staining of myosin-II peptide maps; competitive binding analysis and direct localization in the electron microscope (Fig. 1). Antibodies M2.3, M2.9 and M2.12 bind to distinct and non-overlapping sites on the tip of the myosin-II tail. Antibodies M2.1 and M2.10 bind to different sites on the myosin-II heads. We established previously that M2.1, M2.10, M2.3 and M2.9, but not M2.12, all inhibit by 80–100% both the actin-activated Mg^{2+} -ATPase of myosin-II and the contraction of gelled extracts of *Acanthamoeba* cytoplasm (manuscript in preparation). Maximum inhibition requires the binding of ~1 to 2 antibody molecules per myosin-II molecule. M2.3 and M2.9,

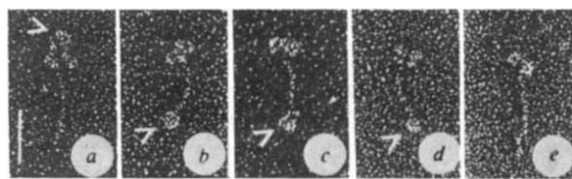


Fig. 1 Electron micrographs of platinum-shadowed complexes of myosin-II molecules with the following antibodies: *a*, M2.1; *b*, M2.3; *c*, M2.9; *d*, M2.12; *e*, Alice, a control monoclonal antibody that does not bind to myosin-II. Arrowheads indicate bound antibody. Scale bar, 50 nm.

Methods: Antibody-myosin-II mixtures were prepared, mixed with an equal volume of glycerol, sprayed onto freshly cleaved mica, dried *in vacuo*, platinum rotary-shadowed, stabilized with carbon and floated onto 300 mesh copper electron microscope grids as described elsewhere (in preparation). Specimens contained a threefold molar excess of antibody over myosin-II. Electron micrographs were taken on a JEOL 100 CX microscope at magnification $\times 23,000$ or $\times 28,000$.

two of the three antibodies that bind to the tail, also inhibit the polymerization of myosin-II into thin bipolar filaments, prevent the lateral aggregation of preformed thin bipolar filaments into thick bipolar filaments, and can disassemble both thin and thick bipolar filaments (manuscript in preparation). As M2.12 inhibits neither polymerization nor actomyosin-II ATPase activity, we thought that inhibition of polymerization by M2.3 and M2.9 might be responsible for their ability to inhibit the ATPase activity. This interpretation is supported by the following detailed analysis of the mechanism of action of M2.1 and M2.3.

The time course of inhibition of the actomyosin-II ATPase by M2.3 differs dramatically from that by antibodies against the myosin-II head, such as M2.1 (Fig. 2) and M2.10 (similar data not shown). After a 30 min preincubation of myosin-II with a 10-fold molar excess of M2.1, M2.3 or M2.10 in 20% sucrose buffer, the steady-state actomyosin-II ATPase activity is inhibited by 80–100%. The inhibition by M2.1 and M2.10 occurs immediately and completely when a 10-fold excess of antibody is added to myosin-II that is actively hydrolysing Mg^{2+} -ATP in the presence of actin (Fig. 2*a*). On the other hand, several hours are required for M2.3 to inhibit maximally the actomyosin-II ATPase in these conditions (Fig. 2*b*). The mechanism by which M2.3 inhibits actomyosin-II ATPase activity must be fundamentally different from the mechanisms of M2.1 and M2.10.

Inhibition of actomyosin-II ATPase activity by M2.3 correlates closely with the disassembly of both thin bipolar filaments in the absence of Mg^{2+} and thick bipolar filaments in 7.5 mM Mg^{2+} (Fig. 3). Considering first experiments in which myosin-II thin bipolar filaments are preincubated in storage buffer (no Mg^{2+} ions; see Fig. 2) with antibody M2.3 (Fig. 3), we observe rapid loss of thin bipolar filaments and actomyosin-II ATPase activity ($t_{1/2} \sim 5$ –10 min). We obtain a good estimate of the activity following each time of preincubation of antibody and thin bipolar filaments, because the ATPase activity was measured in assay conditions that almost completely arrest the disassembly process: the antibody prevents the formation of thick bipolar filaments by the $MgCl_2$, while the $MgCl_2$ retards disassembly of the filaments by the antibody (as judged by electron microscopy, data not shown). Figure 3 demonstrates that when the thin bipolar filaments are preincubated with antibody for ≤ 0.5 min, they have actomyosin-II ATPase activity comparable to thick bipolar filaments and antibody. This activity is four to seven times higher than the activity after the filaments are fully dissociated by the antibody.

Compared with thin bipolar filaments, thick bipolar myosin-II filaments in 7.5 mM $MgCl_2$ are much more resistant to depolymerization and inhibition of the actin-activated Mg^{2+} -ATPase by the M2.3 antibody ($t_{1/2} \sim 3$ h). Fifteen hours of preincubation are required for complete disassembly of the myosin-II thick bipolar filaments and maximum inhibition of the actomyosin-II

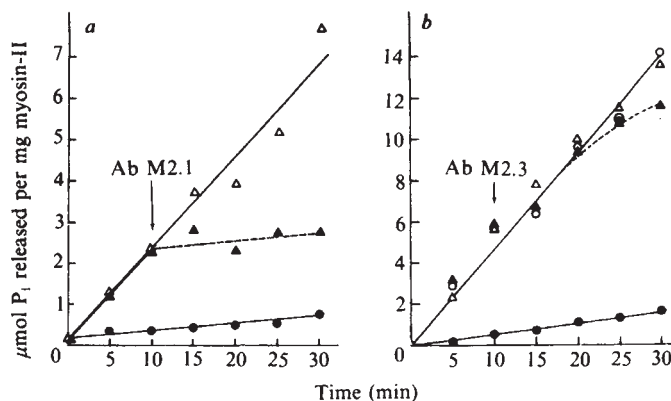


Fig. 2 Time course of the inhibition of actomyosin-II ATPase activity by antibodies M2.1 and M2.3. *a*: ●, Myosin-II preincubated with antibody M2.1 for ~ 60 min at 0°C ; ▲, antibody M2.1 added to actomyosin-II actively hydrolysing ATP 10 min after the start of the assay, as indicated by the arrow; △, antibody buffer added to actomyosin-II 10 min after the start of the assay. *b*: ●, Myosin-II preincubated with antibody M2.3 for ~ 60 min at 0°C ; ○, myosin-II preincubated with antibody buffer ~ 60 min at 0°C ; ▲, antibody M2.3 added to actomyosin-II actively hydrolysing ATP 10 min after the start of the assay as indicated by the arrow; △, antibody buffer added to actomyosin-II 10 min after the start of the assay.

Methods: Myosin-II was purified and dephosphorylated by established protocols^{14,15}. It was stored as thin bipolar filaments in a buffer that preserves enzymatic activity for several weeks (sucrose storage buffer: 20% sucrose, 5 mM imidazole, pH 7.0, 3 mM Na₂S₂O₃ and 1 mM dithiothreitol). For the pre-incubation, 20 μl of myosin (0.43 μM) thin bipolar filaments in sucrose storage buffer and 20 μl of 4.3 μM antibody in sucrose storage buffer without dithiothreitol were mixed and incubated on ice for ~ 60 min. Actomyosin-II ATPase activity was assayed by a method described elsewhere (in preparation). Actin-activated ATPase activity was measured by adding 360 μl of buffer containing actin, appropriate salts, and [γ -³²P]ATP in the presence of unlabelled ATP. Final assay conditions were 10 mM imidazole pH 7.0, 7 mM $MgCl_2$, 0.1 mM $CaCl_2$, 0.5 mM ATP and 12 μM *Acanthamoeba* actin. In these conditions myosin-II forms thick bipolar filaments. The amount of released inorganic ³²P was determined as described elsewhere (in preparation). Actomyosin-II ATPase rate was calculated by subtracting hydrolysis due to myosin-II and actin alone and was typically responsible for $>93\%$ of the ATP hydrolysed in these samples. The release of inorganic phosphate (P_i) is plotted as a function of time.

ATPase activity (Fig. 3). Again, there is a good correlation between the number of filaments observed and the actin-activated ATPase activity following addition of antibody M2.3 to myosin thick bipolar filament preparations. When all of the filaments have disappeared, the ATPase activity is 10–20% of control values, similar to the samples of thin bipolar filaments preincubated with M2.3 in the absence of Mg^{2+} .

The inhibition of actomyosin ATPase activity and myosin-II depolymerization to a similar extent by M2.3 Fab fragments (data not shown) and whole antibody suggests that the above results are not simply due to the cross-linking of myosin-II determinants and consequent myosin-II precipitation. Antibody M2.12 provides an important control: binding of this antibody to a site adjacent to the M2.3 site has minimal effects on either polymerization or actomyosin ATPase activity.

Monoclonal antibodies that inhibit filament formation demonstrate directly that depolymerized myosin-II with a low level of heavy-chain phosphorylation has a low level of actin-activated Mg^{2+} -ATPase (50–100 nmol $\text{mg}^{-1} \text{min}^{-1}$). This activity is stimulated 5–10-fold by polymerization of myosin into thin or thick bipolar filaments. Stimulation of ATPase activity by myosin polymerization occurs independently of any changes in the state of phosphorylation of myosin-II or in the solution

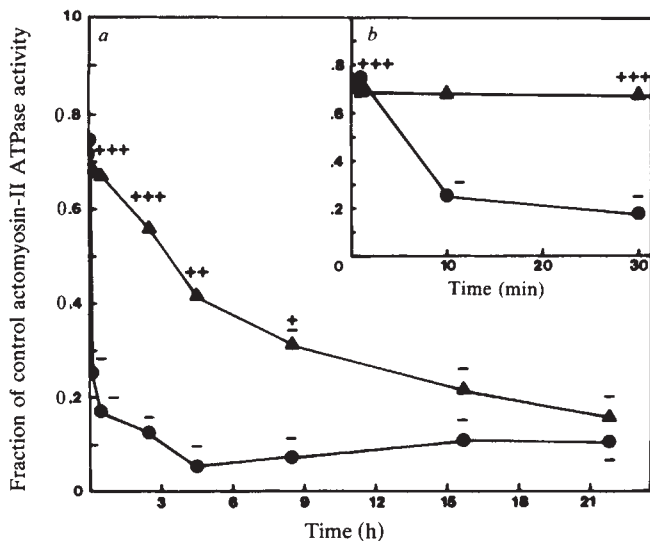


Fig. 3 Time course of the concomitant loss of ATPase activity and depolymerization of filaments during pre-incubation of myosin-II with antibody M2.3. Myosin-II thin (●) or thick (▲) filaments were incubated with a 10-fold molar excess of antibody M2.3 over myosin for various times, then parallel aliquots were assayed either for actin-activated ATPase activity or for filament concentration. ATPase activity is expressed as the fraction of control activity, measured in the absence of antibody. The filament concentration is scored semiquantitatively (+++ to -) next to each ATPase point. In these pre-incubation experiments, the actin-activated ATPase that we measure is inhibited by ~30% as early as the zero time point, whether antibody is mixed with thin bipolar filaments in the absence of Mg^{2+} or with thick bipolar filaments in 7.5 mM Mg^{2+} . This apparent partial inhibition at short times of pre-incubation is due to slow, antibody-induced loss of activity during the ATPase assay (Fig. 2 b, ▲). During preincubation, when ATP is absent, the thick filaments and the ATPase activity are stable for more than 30 min in identical concentrations of $MgCl_2$ and antibody. We conclude that ATP in the assay makes the filaments more sensitive to depolymerization by antibody. These observations concur with the observation that Mg^{2+} -ATP decreases the stability of dephosphorylated myosin-II filaments¹⁸.

Methods: For the pre-incubation, myosin-II thin filaments (no Mg^{2+}) were preincubated with antibody M2.3 as described in Fig. 2 legend. Myosin-II thick filaments were formed from thin filaments by the addition of $MgCl_2$ to 8 mM, then preincubated with antibody M2.3 as described for the thin filaments. Controls included incubation with antibody buffer alone or with antibody that did not react with myosin-II. Actin-activated ATPase activity was assayed as described in Fig. 2 legend, except that the final Mg^{2+} concentration during the assay was 7.5 mM instead of 7 mM for all samples. For the estimation of the filament concentration, following preincubation a small aliquot of the antibody-myosin-II mixture was applied to a glow-discharged, carbon-coated grid, then negatively stained with uranyl acetate as described elsewhere (manuscript in preparation). Electron micrographs at magnifications of $\times 33,000$ to $\times 50,000$ were taken by a microscopist unaware of the history of each sample. The concentration of filaments was estimated from the micrographs and scored semiquantitatively by an unbiased observer who was unaware of the origin of each print.

conditions. The same may be true for other types of myosin, but has not yet been tested directly. The actin-activated ATPase activities of mini-filaments of intact skeletal myosin and of myosin heads isolated after proteolytic digestion are reported to be almost identical¹⁶. However, these results do not exclude the possibility that the ATPase activity of intact skeletal muscle myosin is influenced by polymerization, because proteolysis may alter the function of the isolated heads, or may remove regulation by polymerization concomitant with removal of the myosin tails. As described above, direct analysis of the effect of polymerization of smooth muscle or vertebrate cytoplasmic myosins on their actomyosin ATPase activities, independent of changes

in the state of phosphorylation or in the solution conditions, has not been reported.

Our new observations suggest that myosin-II polymerization could influence contraction in two ways: by effecting the formation of bipolar filaments that are probably structurally essential for some types of movement, or by directly stimulating the cycle of actin-myosin interaction necessary for mechanochemical energy transduction. Any mechanism, including phosphorylation, that regulates polymerization would in turn influence myosin function by either or both mechanisms. We speculate that such coupling of polymerization and stimulation of actomyosin ATPase activity may be unique to cytoplasmic contractile systems, where the cell is required to recruit myosin for transient functions in local regions of the cell. This contrasts with smooth muscle, where both resting and contracting cells contain myosin thick filaments¹⁷, phosphorylation of myosin light chains⁷⁻⁹ must take place on pre-existing myosin filaments, and stimulation of actomyosin ATPase activity is probably independent of gross changes in myosin polymerization. In non-muscle systems the question remains as to whether phosphorylation influences the actomyosin ATPase simply by effects on polymerization.

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Corrigendum

The gait of *Hipparion* sp. from fossil footprints in Laetoli, Tanzania

E. Renders

Nature **308**, 179-181 (1984)

IN line 17 of the penultimate paragraph on page 180, the speed of the adult *Hipparion* should be 6.5-8 km h⁻¹, not 10 km h⁻¹ as given.